UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

BTG INTERNATIONAL LIMITED, et al., Plaintiffs, vs. AMNEAL PHARMACEUTICALS LLC, et al., Defendants.

TRANSCRIPT OF TRIAL PROCEEDINGS

Volume 4, Pages 751-988

HONORABLE KEVIN McNULTY, USDJ
Civil Action No. 2:15-cv-5909-KM-JBC

BTG INTERNATIONAL LIMITED, et al., Plaintiffs, vs. AMERIGEN PHARMACEUTICALS, INC., Defendants.

HONORABLE KEVIN McNULTY, USDJ
Civil Action No. 2:16-cv-2449-KM-JBC

BTG INTERNATIONAL LIMITED, et al., Plaintiffs, vs. TEVA PHARMACEUTICALS USA, INC., Defendants.

HONORABLE KEVIN McNULTY, USDJ
Civil Action No. 2:17-cv-06435-KM-JBC

MARTIN LUTHER KING BUILDING and U.S. COURTHOUSE
50 Walnut Street, Newark, New Jersey 07101
Thursday, July 26, 2018
Commencing at 9:00 a.m.

B E F O R E:

THE HONORABLE KEVIN McNULTY
UNITED STATES DISTRICT JUDGE

Certified as true and correct as required by Title 28, U.S.C., Section 753.

/S/Rhéa C. Villanti, CCR, CRCR, CLR

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EXHIBITS

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EXHIBITS

NUMBER	MARKED	RECEIVED
PTX 454		825
PTX 455		825
PTX 456		825
PTX 457		825
PTX 074	074	
PTX 459	906	

(In open court with counsel present.)

THE CLERK: All rise.

THE COURT: Good morning, everyone.

Be seated. Ready?

AKHILESH NAGAICH, Ph.D., DEFENDANTS' WITNESS,

having been duly sworn, continued to testify as follows:

THE COURT: The witness, of course, is still under oath. I am sure you know that.

MR. REIN: We can wait until the witness is done.

THE COURT: Wait until a convenient break to do the exhibits, sure.

MR. WONG: Mr. Wong for the record, Your Honor, Jovial Wong from Winston Strawn.

(CONTINUED DIRECT EXAMINATION)

BY MR. WONG:

Q. Good morning, Dr. Nagaich.

A. Good morning.

Q. I think when we left off yesterday, I think you said you reviewed the pertinent regulatory documents filed in support of Zytiga®'s NDA approval.

Do you recall that?

A. Yes.

Q. So let's look at what we had up on the screen. This is DDX 210015.

What is shown on the screen?

A. This is a timeline for regulatory approval of Zytiga® starting from the IND filing in 2005, all the way until the final approval in 2018 --
Q. You mentioned --
A. -- this year.
Q. You mentioned approval. We have been talking about a few approvals of Zytiga®. Can you just identify for the Court which dates Zytiga® was actually approved.
A. So Zytiga® was first approved on April 28, 2011. And then subsequently, it was approved in December -- on December 10, 2012. And then finally on February 8, 2018, for a new indication of metastatic hormone-sensitive prostate cancer.
Q. Okay. Let's start from the beginning. Let's look at the IND filing. Had you reviewed the pertinent documents surrounding IND filing in 2005?
A. Yes.
Q. Let's look at DTX 1327.
A. Okay.
Q. I don't think we have seen this in court yet. So, Dr. Nagaich, do you recognize this document?
A. Yes, I do.
Q. What is it?
A. This is a pre-IND meeting briefing package that Cougar Biotechnology submitted to the FDA.
Q. Now, when would this have been submitted to FDA?

A. I believe this must have been submitted before the IND filing, so in 2005 sometime.
Q. What is a pre-IND meeting?
A. The pre-IND meeting is an initial meeting of a sponsor with FDA to get feedback from FDA regarding their clinical and development program and product development program.
Q. When you worked at FDA, were you involved in a pre-IND meeting with applicants?
A. Yes, many such meetings.
Q. So what is a pre-IND meeting package, then?
A. The package is before seeking out a face-to-face meeting with FDA, a sponsor is required to submit a briefing package to educate the reviewers regarding the product that they are trying to double up and also discuss any potential questions that they would like to discuss with the agency.
Q. Okay. Let's take a look at this document.
MR. WONG: Can we go to page 9 of the document.
BY MR. WONG:
Q. There's a heading, 1.2, Meeting Objectives. Do you see that?
A. Yes.
Q. So what does this say about the meeting objectives for the pre-IND meeting?
A. The objective for this pre-IND meeting are to obtain input from the Food and Drug Administration on the specific questions

for discussion presented in the section 1.5.

MR. WONG: Let's take a look at those questions. Can we go to page 11 of the document.

BY MR. WONG:

Q. There's a Table 1 here. What is listed in this table?

A. This table lists the specific questions that Cougar wanted to discuss with the FDA regarding the clinical development, chemistry, manufacturing, and controls, and the non-clinical development of the program.

Q. So do any of Janssen's questions here relate to the role of prednisone when used with abiraterone?

A. Yes, it does. If you look at the question third in the clinical development section, it says: Does the FDA agree that a steroid supplementation will be given on as-needed basis?

Q. How does this inform your opinion, Doctor?

A. This says that Janssen was not -- Cougar was not initially looking forward to using steroid supplementation on -- with abiraterone acetate on a regular basis. It was -- they were thinking of giving this as needed.

Q. Okay. And if Cougar intended to use prednisone or a steroid as an anti-cancer agent, would they have asked such a question to FDA, in your opinion?

A. No. Then in that case this question would not make sense.

Q. Now, Doctor, did FDA ever provide an answer to Cougar's question number 3?

A. Yes, it did.

MR. WONG: Let's take look DTX 1326.

BY MR. WONG:

Q. I think we've seen this document. But, Doctor, what is this document?

A. This is a letter from FDA to Cato Research, a representative of Cougar.

Q. In the second paragraph, does it discuss the pre-IND meeting?

A. Yes. It says: We also refer to the meeting between representatives of your firm and the FDA on April 18, 2005.

Q. Let's go to page 2. What is the heading of page 2?

A. It says: Memorandum of Meeting Minutes. The meeting date is April 18, 2005.

Q. Now, just to be clear, who prepared these meeting minutes?

A. This meeting minute was prepared by FDA to capture the discussions in their face-to-face meeting.

MR. WONG: Let's go to page 7 of these FDA meeting minutes.

Sorry. Page 6. Yup. Sorry.

BY MR. WONG:

Q. On page 6, let's look at the bottom. There's a heading that says: Question No. 3.

The question reads: Does the FDA agree that steroid supplementation will be given on an as-needed basis?

Do you see that?
A. Yes, sir.
Q. That's the question Cougar posed to FDA?
A. Yes.
Q. So how does FDA answer that question?
A. FDA said no. It explained the results from study C reported in the literature showed that all 3 patients in the 500-milligram group in study C had abnormal ACTH stimulation tests on day 11, while all 3 subjects on the 800-milligram group had both abnormal ACTH stimulation tests and significantly lower evening cortisol levels on day 11, compared to baseline levels.
Q. And based on this finding by FDA of a study C, what does FDA say?
A. It says further that this reflects a potential meaningful effect of abiraterone on the production of glucocorticoids.
It says that in the proposed single-dose study, strict monitoring of mineralocorticoid and glucocorticoid production is advised.
Q. Okay.
A. Yeah.
Q. But can you read the sentence "based on these results" right in the middle. What does FDA say there?
A. Yes. Says: Based upon these results and in conjunction with the division of metabolic and endocrine drug products, the

division believes that empiric supplemental steroids should be given to all patients during any multi-dose study.

Q. And then does FDA further elaborate on their understanding in the additional discussion?

A. Yes. In further discussions, FDA says that the division reiterated that steroid supplementation should be given during any multi-dosing with abiraterone, and Cougar agreed.

Q. So, Doctor, what does this tell you about FDA's understanding of the role of prednisone when used with abiraterone, starting in 2005?

A. The FDA was concerned about the side effect of Zytiga®, particularly the abnormal ACTH stimulation. And they wanted Cougar to give prednisone on -- should be given to all patients during any multi-dose study, should be given with abiraterone acetate.

Q. And just to be clear for the record, it doesn't say prednisone here, right?

A. It doesn't say prednisone.

Q. It just says steroid supplementation --

A. Right.

Q. -- just so we're clear.

But is there anything here in FDA's response to Cougar's question to suggest that it considered steroids or prednisone to have any anti-cancer role when combined with abiraterone?

A. No.
Q. Now, have you seen other documents reflecting what was discussed at this April 18, 2005 pre-IND meeting between Cougar and FDA?
A. Yes.
Q. Let's go to DTX 1323. I think we have seen this document before with Ms. O'Shea.
Do you recall that?
A. Yes, I do.
Q. And these are Cougar's meeting minutes of that same meeting, right?
A. That's correct.
Q. Now, why would Cougar be preparing meeting minutes of the same pre-IND meeting?
A. This is the usual practice that sponsors -- they also capture the meeting minutes, and they share their version of the meeting minutes with the agency to make sure that everybody is on the same page.
Q. Right. Let's go to page 7 and see what they say.
MR. WONG: Let's highlight Paragraph 3.
BY MR. WONG:
Q. So, Doctor, what is written here in this third paragraph on page 7?
A. This paragraph captures a discussion that Cougar had with FDA. And it says that Theresa Kehoe, who was the medical and

clinical reviewer for this pre-IND, asked what Cougar intends to use as a glucocorticoid supplementation.

Then she explained that FDA's concern is mineralocorticoid excess and suggested Cougar use glucocorticoids with minimal mineralocorticoid effects, such as prednisone rather than hydroxycortisone.

She further warned that patients could become hypotensive and hypokalemic and wanted mineralocorticoid excess to be which glucocorticoid should be used in this study. Theresa Kehoe recommended that prednisone be used.

Q. Okay. So what does this tell you -- what does this further tell you about what Cougar and FDA discussed at this meeting with respect to the role of a steroid like prednisone in combination with abiraterone?

A. The discussion focused only on the side effects associated with Zytiga® --

Q. Okay.

A. -- and how prednisone should be used to tackle the side effects.

Q. Okay. In any of the meeting minutes for the April 2005 pre-IND meeting for Zytiga®, did you see any proposal from Janssen that prednisone had -- or any other steroids had anti-cancer efficacy?

A. No, I have not seen any evidence.

Q. Did you see any acknowledgment by FDA that prednisone or

any steroid had any anti-cancer efficacy when used with abiraterone?

A. No, I have not seen.

Q. Let's go back to the timeline. So we just took a look at 2005.

Doctor, let me ask you this: Did FDA eventually approve Cougar's IND to allow them to begin human clinical trials?

A. Yes.

Q. Were you in the courtroom when Dr. Charnas reviewed those clinical trials with the Court?

A. Yes.

Q. Do you understand during one of the phase I clinical trials, unfortunately, there was a patient death who was receiving abiraterone monotherapy?

A. Yes, I heard that. Yes.

Q. Now, as a result of that patient death, what did Cougar do with respect to all of its ongoing trials with abiraterone?

A. They modified their clinical protocol and concluded that the prednisone be administered with all the patients.

MR. WONG: Let's look at DTX 1367, which we saw with Dr. Charnas a couple days ago.

BY MR. WONG:

Q. Do you remember this document?

A. Yes, I do.

Q. This is the clinical study report for Cougar, the 002 study, right?
A. That's correct.
Q. So does this document describe the reason why Cougar added prednisone to its clinical trials following the death?
A. Yes, it does.
MR. WONG: Let's go to page 23.
BY MR. WONG:
Q. You see this is a continuation of various amendments that were made to the protocol. Let's look at amendment 7 dated 8 or 6 October 2008.
Can you read the first bullet point, please?
A. Yes. It says: Required all subjects in phase I to receive abiraterone acetate in fasted condition with low-dose glucocorticoid.
Q. And is it your understanding that this amendment 7 was made in response to the patient death?
A. Yes.
Q. Does this phase II clinical study report document for the 002 study further describe the reason Cougar added prednisone as part of amendment 7?
A. Yes.
MR. WONG: Let's look at page 19.
BY MR. WONG:
Q. So what is -- first of all, what is described generally

here in this section 3 -- 3.11?
A. This describes the overall design for their phase I and phase II studies.
Q. So let's see what Cougar says about their phase II study design.
MR. WONG: Blow up the bottom paragraph.
BY MR. WONG:
Q. Doctor, I think there's a reference to amendment 7 in the last sentence. Can you read that.
A. It says: Following amendment 7 of the protocol, all subjects were required to receive low-dose glucocorticoid, such as prednisone 5 milligrams twice daily PO or dexamethasone .5 milligram once daily, with abiraterone acetate to better manage mineralocorticoid side effects.
Q. So what does this tell you?
A. This tells that -- that this protocol was amended and all patients were required to have prednisone to manage mineralocorticoid side effects.
Q. Is there any description here that the role of prednisone, when it was added to the combination, was to provide an anti-cancer effect --
A. No.
Q. -- to patients?
And were you in the courtroom when Dr. Charnas was testifying about this document?

A. Yes.
Q. I think he suggested that amendment 5 reflected Cougar's decision to add prednisone to the combination for efficacy reasons. Do you recall that?
A. Yes.
MR. WONG: Let's look at amendment 5 again. I believe that's on page 22. Blow up the bottom.
BY MR. WONG:
Q. There's a listing here in this clinical study report that says, amendment 5, 25 May 2007. Do you see that?
A. Yes, I see that.
Q. So what is Cougar telling FDA here about why they made amendment 5 to the protocol?
A. This is simply to their COU-AA-001 study, and there is no submission that they required in this amendment addition of prednisone.
Q. So, Doctor, is there any description here in either of these three bullet points that shows Janssen telling FDA that they have found that prednisone provides an anti-cancer effect in the combination?
A. No.
Q. Let's go back to the timeline. So after Cougar finished its clinical trials, did Cougar file its NDA for Zytiga®?
A. Yes; filed NDA for Zytiga® on December 10, 2010.
Q. And, Dr. Nagaich, did you review the pertinent parts of

Janssen's NDA submission in forming your opinions?
A. Yes, I did.
Q. Let's take a look at DTX 8187. And we've seen this document, too, with Dr. Charnas. Do you remember?
A. Yes.
Q. So this document is the summary of clinical efficacy. Do you see that at the top?
A. Yes.
Q. And this was submitted with Janssen's Zytiga® NDA?
A. Yes.
Q. So what is the purpose of the summary of clinical efficacy document in the NDA?
A. The summary of clinical efficacy document is an integrated analysis and summary of all the clinical trial data that is submitted with NDA. It is part of the module to -- of the NDA.
Q. And so in terms of efficacy of the drug product, the NDA drug product, would it be described in this document?
A. Yes. This -- yes, it would be described.
Q. So -- and to be clear, do you have experience reviewing this type of document during your time at FDA?
A. Yes, I have.
Q. About how many summary of clinical efficacy reports have you reviewed?
A. I have reviewed about eight of these at the FDA.
Q. Let's go back to page 9. We've seen this before. This is

Section 1.1, right off the bat. And Section 1.1 says: Design of clinical studies providing the basis for efficacy.

Do you see that?

A. Yes, I see that.

Q. What is the purpose of this section?

A. This section lists all the studies that form -- that are providing the basis for efficacy.

Q. Okay. And what does it say in the first sentence?

A. The following clinical studies evaluated the efficacy of abiraterone acetate at the 1 gram daily dose and are included in this summary of clinical efficacy.

Q. So is Janssen telling FDA that these studies evaluate the efficacy of abiraterone acetate at a specific dose?

A. Yes.

Q. Let's take a look at the clinical trials listed here. Let's take a look at the first study -- you can leave it up. The first study is the phase III 301 study. Do you see that?

A. Yes, that's right.

Q. What is the significance of the designation that the phase III Cougar 301 study is the pivotal study?

A. Well, this is the pivotal study that is the basis for granting FDA approval. This is an adequate and well-controlled study to grant approval for Zytiga®.

Q. Okay. And per the regulations we reviewed yesterday, is Janssen telling FDA that this study has a substantial evidence

of effectiveness of Zytiga® that should be used for granting approval?
A. Yes.
Q. There was some discussion in court as to the purpose of these studies listed here. What about the other studies? Why does Janssen include the other phase I and phase II studies here?
A. These are included because Janssen has paid out other studies --
THE COURT REPORTER: Has what out?
A. -- other studies dosing requirement, PK/PD requirements, and other developmental studies are listed but these studies do not form the basis for the approval.
Q. So are the phase I and phase II trials listed here adequate and well-controlled?
A. No.
Q. And how do you know that?
A. These studies are not adequate. They require randomized blinded studies in a large subject population to claim -- for the efficacy claims on your label, and none of these studies are.
Q. What about the control aspect? How are these -- are these phase I and phase II studies properly controlled to support approval?
A. No, these are not adequate and well-controlled studies for

the granting of the labeling claims.
Q. So would the phase I and phase II trials, would any of them be able to provide substantial evidence of effectiveness of Zytiga®?
A. No.
Q. Okay. What about with respect to prednisone in combination with Zytiga®? Would any of these phase I and phase II trials be able to provide substantial evidence of that?
A. No, not at all.
Q. And what about -- let's go down to the bottom one. What about the phase I Cougar-001 study that was discussed yesterday?
Just to be clear, was that an adequate and well-controlled study that could provide substantial evidence of effectiveness to support the indication?
A. The 001 study was not well-controlled and adequate a study.
Q. Does the 001 study even provide any evidence of survival benefit?
A. No.
Q. What does it provide evidence of? Or what was the data that -- the endpoints of the 001 trial?
A. They were using PSA as a marker, and PSA is not a reliable marker to predict clinical efficacy --

Q. From a regulatory --
A. From the regulatory point of view.
Q. Do you recall the discussion yesterday with Dr. Rettig about cross-comparisons of studies?
A. Right.
Q. In your review of the NDA documents was any cross-comparison study of the 001 versus 002 studies ever presented to FDA as a basis for supporting Zytiga®'s indication?
A. No.
Q. Would a cross-comparison study of the 001 versus 002 studies even be considered as an adequate and well-controlled study?
A. No.
Q. Why not?
A. They would not be considered for granting approval.
Q. There's also been a lot of discussion in court -- and review about scientific articles that Janssen published with respect to Zytiga®?
A. Right.
Q. Were you here for that?
A. Uh-huh.
Q. Does FDA consider and review data and descriptions in scientific articles as a basis for approving drugs?
A. No. Scientific articles are not submitted along with NDA

or -- NDA applications.
Q. But even if they were submitted with the NDA, would FDA consider that as a basis for approval when making that determination?
A. No, not at all.
Q. Just to be clear, in your review of the regulatory documents do you recall either Janssen or FDA ever relying on scientific articles for Zytiga® as the basis for the approval of Zytiga®?
A. No.
Q. Now -- and to be clear, does this -- going back to what's listed here in 1.1, does this section review in any way the clinical studies that might provide the basis for efficacy of prednisone when taken in the combination?
A. No.
Q. Now, if Janssen were seeking to have FDA approve the use of prednisone to provide anti-cancer efficacy with Zytiga®, would this section right here look different?
A. Yes. This section would have -- look differently. They would have added prednisone right here in the first sentence, that they plan to discuss efficacy of abiraterone acetate and prednisone.
Q. If they were making that claim to FDA, would further trials also have to have been conducted and listed here?
A. Absolutely. Yes.

MR. WONG: Let's go to page 54.
BY MR. WONG:
Q. I think we also talked about this page with Dr. Charnas. What is described -- let's look at the bottom starting on Section 4.
What's the title, sir?
A. It says: Analysis of clinical information relevant to dosing recommendations.
Q. What is the purpose of this section? What is Janssen telling FDA here?
A. This describes the rationale for dose selection.
Q. For --
A. Abiraterone acetate and prednisone.
Q. So let's look at the first paragraph. How is the dose of abiraterone selected?
A. Janssen did a -- or Cougar did a dose escalation study, and based on that, those escalation study, they selected a daily dose of 1 gram of abiraterone acetate; and that dose was supported by their pharmacokinetic, pharmacodynamic, and efficacy data.
Q. Why does a company require -- why does a company do a dose escalation study on the drug they're looking for approval for?
A. The dose escalation study is required to -- for -- to find out what is the maximum tolerated dose and what is -- would be an appropriate dose based on -- where it doesn't cause toxicity

and what is the best dose for efficacy.
Q. So that's how they determine the abiraterone dose.
Let's look at the second paragraph. Does it describe here how they determine the dose for prednisone?
A. Yes, it does.
Q. Let's read the first sentence of the second paragraph.
A. It says: Concurrent treatment with prednisone 5 milligrams twice daily is administered to ameliorate mineralocorticoid-related toxicity that was observed with abiraterone acetate in early phase I/II studies.
Q. So is Janssen telling FDA here that this is the basis for using 5 milligrams twice daily dose with abiraterone?
A. Yes.
Q. Now, was a dose escalating study ever performed for prednisone?
A. No. The dose escalation study was not performed.
Q. Now, if Janssen were seeking approval from FDA for anti-cancer effects of prednisone when used with Zytiga®, would FDA have expected to see a dose finding study here for prednisone?
A. Absolutely. I think if they were seeking approval of prednisone as an anti-cancer, it is required that you do a dose escalation study to find out what is the optimum dose and, you know, is there a toxicity associated with it. So FDA would have expected it.

Q. In your review of the NDA documents did you see Janssen ever looking at such an issue for prednisone?
A. No, I have not seen any evidence for that.
Q. So aside from ameliorating side effects of abiraterone, is there anything in the summary of clinical efficacy document that discusses the role of prednisone as an anti-cancer agent?
A. No, there is nothing in the summary of efficacy document that talks about efficacy of prednisone.
Q. Okay. So take a step back.
This is Janssen's NDA for Zytiga®, right?
A. Right, this is Janssen's NDA for Zytiga®.
Q. And because Janssen only described the role of prednisone for safety in this document, what does that mean with respect to FDA's approval of Zytiga®?
A. That FDA approved Zytiga® as an anti-cancer drug and prednisone's role was to -- for the safety.
Q. Okay. And, again, based on your experience at FDA reviewing these types of summary of clinical efficacy documents, if Janssen were asking FDA to approve prednisone for its anti-cancer effects in combination, would this submission, this document, have looked different?
A. Yes, absolutely. There would have been a lot of discussion about positioning prednisone as -- in its anti-cancer role. There would have been studies supporting that prednisone has anti-cancer activity.

Q. And when you were in court, did you hear discussion about Dr. de Bono -- were you here for Dr. de Bono's testimony?
A. Yes, I was.
Q. And over the past couple days have you heard discussion about Dr. de Bono's hypothesis that led him to the 001 trial?
A. Yes, I heard that.
Q. Can we call this the de Bono hypothesis?
A. Yes.
Q. Was there any description in this summary of clinical trials document of Dr. de Bono's hypothesis?
A. No, I have not seen any discussion of the hypothesis.
Q. Let's go back to the timeline.

So Janssen filed its NDA in 2010. When was Zytiga® first approved?
A. Zytiga® was approved on April 28, 2011 for mCRPC for patients who had a prior treatment of docetaxel.
Q. And was there anything in the 2011 approval package that described FDA's understanding of the role of prednisone when administered with Zytiga®?
A. Yes.
Q. Let's look at DTX 1336. And I think we've also seen this document with Dr. Charnas. It's titled Office Director Memo. Do you see that?
A. Yes.
Q. Let's go to page 2. Let's go to the -- page 2, please.

Let's go to that first chart, the first box. It says Office Director Memo -- Office Director Decision Memo. Do you see that?
A. Yes.
Q. What is this document?
A. This is a memo from the office director. This memo forms the basis for the approval letter.
Q. Okay. At the bottom you see it says action/recommended action for NME? You see that?
A. Yes.
Q. And it says approval?
A. Yes.
Q. Let's go to page 3. Let's look at that Section 2. That's titled Clinical Efficacy. Do you see that?
A. Yes.
Q. So what's the purpose of this section?
A. This section summarizes the clinical efficacy data for Zytiga®'s NDA.
Q. Okay. And let's -- can you read the first sentence, please.
A. It says: This application is supported by the results of a randomized, placebo-controlled, multi-center trial in 1,195 patients with metastatic CRPC previously treated with docetaxel-containing regimens.
Q. All right. And this is the 301 study?

A. Yes.
Q. And only the 301 study was the pivotal study, right?
A. That's right.
Q. What does it say in the next sentence?
A. The patients were randomly allocated 2 to 1 to receive either abiraterone acetate orally at a dose of 1,000 milligram once daily or placebo once daily.
Q. And does the next sentence acknowledge the role of prednisone in the study?
A. Yes. It says: Patients in both arms received prednisone 5 milligram orally twice daily.
Q. So what do you conclude here as far as FDA's understanding of the 301 study?
A. That FDA approved of Zytiga® as an anti-cancer drug. Prednisone was there for safety reasons. It was their part of the control arm as well as the experimental arm.
Q. Okay. So let's look at the second paragraph. Let's look at the second -- I think this has results. Look at the second line that starts "this analysis." Can you read that?
A. It says: This analysis demonstrated a statistically significant improvement in overall survival in patients receiving abiraterone acetate compared to those on the placebo-containing arm.
Q. Any description here that prednisone contributed or provided any statistically significant improvement in the

overall survival when used with abiraterone acetate?
A. No, there is not.
Q. So is there any indication that FDA concluded that the increase in overall survival of the 301 study was due in any way to prednisone?
A. No.
Q. And when Dr. Charnas testified about this office director memo, do you recall that he suggested that FDA sometimes takes liberties to use shorthand in their communications?
A. No. I disagree with that statement.
Q. Do you recall that statement, though?
A. Yes, I do.
Q. And he suggested that when FDA says "abiraterone" here, they really mean abiraterone plus prednisone, right?
A. No.
Q. Why? Why do you disagree with that?
A. I think these are very carefully drafted memos. They form the basis of the approval. And FDA is very, very careful in they will write what they mean.
Q. Would that be especially true in approval documents like this?
A. Absolutely.
Q. So what is your takeaway from what FDA is saying here in this Section 2 of this approval document?
A. It says that abiraterone acetate is the drug that treats

the cancer, and prednisone is there for safety reasons.
Q. Let's look at page 5. Let's go down to section 6 at the end. We saw this section as well with Dr. Charnas.
A. Yes.
Q. This is entitled Decision/Action/Risk-Benefit Assessment?
A. Right.
Q. So the first title says Regulatory Action: Approval, right?
A. Yes.
Q. Then it goes on to describe a risk-benefit assessment.
What is a risk-benefit assessment?
A. A risk-benefit assessment is carried out based on their phase III data by the clinical review team to really weigh what the benefits are and compare them with the risks associated with the drug.
Q. Let's take a look at the benefits, if you can read the first sentence.
A. It says: The efficacy and safety findings from the clinical review of this NDA provide substantial evidence for the effectiveness of abiraterone acetate in the intended patient population (a 3.9-month improvement in median overall survival compared to placebo) with an acceptable toxicity profile.
Q. Keying in on the word "substantial evidence for effectiveness," that's a requirement from the regulations,

right?
A. That is -- that is correct.
Q. When FDA makes its findings and understandings known about what the substantial evidence for effectiveness that it's approving is, what does it refer to?
A. Zytiga®.
Q. Does it go on -- does this paragraph go on to describe the risks that it found with abiraterone?
A. Yes. In the next sentence, it says: Abiraterone acetate has unique toxicities that include mineralocorticoid excess-associated adverse reactions, adrenal corticoid insufficiency, and hepatotoxicity. And these unique safety issues have been addressed in the product labeling.
Q. What does that tell you about, that last sentence -- These unique safety issues have been addressed in the product labeling -- how does that inform your opinion?
A. That, in the labeling has been -- that these toxicity issues have been addressed in the labeling, and the label has been modified to inform the healthcare providers that there are unique toxicities associated with Zytiga® --
Q. Okay. We will take a look at that labeling in a bit.
In this risk-benefit assessment, is there any discussion by FDA at all that there's any benefit of prednisone in terms of providing efficacy in the combination?
A. The benefit is to address side effects associated with

mineralocorticoid excess.
Q. Okay. Yeah, but with respect to any benefits of efficacy of prednisone in the combination, is there any description here of that?
A. No.
Q. And does FDA at all acknowledge Dr. de Bono's hypothesis here in this risk-benefit assessment?
A. No.
Q. Any mention here that prednisone might be reversing the risk of resistance of abiraterone due to promiscuous AR?
A. No, not at all. No discussion.
Q. So if FDA approved prednisone for the first time for its anti-cancer effects when used in combination with a product like Zytiga®, as Janssen is alleging, do you think it's odd that FDA doesn't even discuss that here in the risk-benefit assessment?
A. Yes. This is very odd because glucocorticoids are a pharmaceutical -- belong to a pharmaceutical class that have never been approved for anti-cancer use. And if FDA was considering that prednisone has anti-cancer effect, then they would have required a lot more data here.
Q. So let's read the last paragraph now that starts "the benefits." Can you read that, please. Starts "the benefits and risks of abiraterone," the last -- can you read that for the record.

A. It says: The benefits and risks of abiraterone were discussed in the division director's summary review, the CDTL and clinical reviews. The review team found the risk-benefit assessment to be acceptable. In conclusion, I concur with Dr. Justice's assessment in his summary review as well as the review team's recommendation for approval.
Q. So here is FDA underscoring that this is the reason why it approved Zytiga®?
A. That is right.
Q. All right. So, Doctor, have you reviewed any documents from the 2012 approval of Zytiga® that describe the role of prednisone?
A. Yes, I have.
MR. WONG: Let's look at DTX 1340. Let's go to page 51.
BY MR. WONG:
Q. We also saw this with Dr. Charnas a couple days ago?
A. Yes.
Q. So what is this document? It's entitled Cross-Discipline Team Leader Review. What is that?
A. This is a review from the cross-discipline team leader on their supplemental NDA.
Q. Were you part of such teams during your time at FDA?
A. Yes.
Q. Let's go to page 53. I think it carries -- I mean bottom

of 53 -- 52 and it carries over to 53. Let's look at what is said here. There's a sentence that starts "however" at the bottom.

Do you see that?

A. Yes.

Q. Would you read that, please.

A. It says: However, a consequence of androgen and cortisol inhibition in the adrenal gland by abiraterone is an increase in adrenocorticotropic hormone release and mineralocorticoid excess. Prednisone has been given with abiraterone to suppress ACTH and to provide needed glucocorticoids.

Q. Okay. What does this tell you about FDA's understanding of the role of prednisone in the 2012 approval of Zytiga®?

A. It just clearly explains why prednisone has been given. It has been given with abiraterone to suppress ACTH and provide needed glucocorticoids that have been depleted.

Q. Does FDA mention here anything about the prednisone's anti-cancer efficacy or Dr. de Bono's theory at all?

A. No.

Q. And this is in the 2012 approval, right, after the first approval of Zytiga® in 2011?

A. That's correct.

Q. Doctor, did you review the entire 2012 FDA approval package?

A. Yes, I have.

Q. Did you see any statement in that approval package that indicated that FDA approved prednisone as an anti-cancer agent when given with abiraterone?
A. No.
MR. WONG: Let's go back to the timeline.
BY MR. WONG:
Q. After Zytiga® was approved in 2012, were there any other significant regulatory events with respect to this NDA? Was there a new approval?
A. Yes. They were seeking out approval of Zytiga® for patients who were pre-docetaxel patients.
Q. And eventually that approval was granted in 2018; is that right?
A. So I think I was confused with -- I think -- yes. This approval was granted in February 8, 2018.
Q. And have you reviewed the relevant parts of Janssen's supplemental NDA submission?
A. Yes.
Q. Do any of Janssen's supplemental NDA submissions show that Janssen asked FDA to approve prednisone as an anti-cancer agent when given with Zytiga®?
A. No.
Q. And let's go back a little bit. I think something was filed in August -- on August 7, 2012.
Do you see that?

A. Yes.
Q. What was filed?
A. They filed an informed consent form.
MR. WONG: Right. Let's take a look at that.
Can we see DTX 1585.
BY MR. WONG:
Q. You saw this document being reviewed with Ms. O'Shea, correct?
A. Yes.
Q. So is this the informed consent form that Janssen gave to patients in 2012?
A. Yes.
Q. What is an informed consent form?
A. The informed consent form is a form that is given to subjects who are considering participating in a clinical trial to inform them about the drug, how the drug works, whether they should participate in the trial or not.
Q. And why do you -- when patients sign up for a clinical trial, why is an informed consent form important to give to a patient?
A. It's important to inform them about all the risks and benefits associated with the trial. It is a requirement by the FDA that participating subjects must be informed.
Q. And just to confirm the date at the bottom, what is the date in the bottom left-hand corner?

A. The date is August 7, 2012.
Q. This is after the first approval of Zytiga® in 2011?
A. Yes.
Q. Let's take on this blow-up -- what -- as the purpose of the study, what does the informed consent form tell patients?
A. It says that Zytiga®, abiraterone acetate, is being studied to see if it may be useful in treating metastatic hormone-naive prostate cancer.
Q. Any mention here about looking to see if prednisone has any anti-cancer effects when combined with Zytiga® in this investigation?
A. No.
Q. So let's go on to page 2. I think they describe prednisone's role. Let's go to page 2. And let's look at that sentence that starts "although." Can you read that?
A. Yes. It says: Although prednisone is commonly prescribed to patients with prostate cancer, it has not been approved to treat this disease.
Q. And is this statement here referring to a prednisone monotherapy indication?
A. It's a very broad statement. It could refer to monotherapy, yes.
Q. Okay. But patients in this LATITUDE trial are not taking prednisone monotherapy, right? They're taking it with Zytiga®.
A. Yes. I think they are -- I think Janssen is telling the

patients that, look, as a monotherapy, also the prednisone is, although commonly prescribed to patients to -- commonly prescribed to patients with prostate cancer and it has not been approved to treat this disease. And it's likely that in the combination, in combination with abiraterone acetate, it could have similar role.

Q. And because this is what Janssen is telling patients in 2012, what does that tell you with respect to the approval of prednisone -- I'm sorry.

What does that tell you about the approval of prednisone with Zytiga® in the original approval in 2011?

A. That tells that -- that prednisone has not been approved as an anti-cancer drug.

Q. If FDA had already approved prednisone for anti-cancer effects in the combination in 2011 like Janssen is alleging, would you have expected Janssen to tell patients that in this informed consent?

A. Absolutely. Patients are -- Janssen would have required to inform patients about that.

Q. Let's go -- but this document does describe actually to patients, actually why they're taking prednisone later, right?

A. Yes.

MR. WONG: Let's go to page 13. Let's blow up the first three paragraphs.

BY MR. WONG:

Q. So in these paragraphs here, what is ascribed -- what is Janssen telling patients as to the role of prednisone that they will be getting?
A. It talks about the side effects of Zytiga®. It says Zytiga® should be used -- says one patient died while taking Zytiga® without prednisone in an early trial. This doctor felt that he died as a result of a heart attack associated with serially low blood potassium and that was primarily related to Zytiga®.
Q. This is in reference to the patient death in the phase I study, right?
A. That's correct.
Q. What do they say in the second paragraph?
A. It says: Preliminary data suggests that the use of medications such as prednisone together with Zytiga®, as will be given to you in this study, can reduce or eliminate some side effects, such as high blood pressure, low blood potassium, and swelling of legs as a result of the body keeping too much fluid.
Q. What about the third paragraph? Anything informing patients as to the role of prednisone?
A. Yes. It says: One of the potential side effects of this study treatment is that it will reduce the production of cortisol, a hormone produced by the adrenal glands.
It further explains that adrenal glands are

responsible for production of several hormones that regulate salt and water retention, blood pressure, sugar levels, et cetera.

Q. What's the next paragraph say -- next sentence.

A. In this study, you will be taking prednisone, a medication that works like cortisol, which may improve the study treatment side effects.

Q. Now, does this informed consent anywhere ever tell prospective patients that prednisone is having an anti-cancer effect?

A. No, not at all.

Q. Now, is that something you would expect to see in an informed consent form if prednisone was indeed providing anti-cancer efficacy when combined with Zytiga® as plaintiffs are alleging?

A. Yes, especially if after their 2011 approval, if Janssen claims that prednisone has been approved as an anti-cancer, they would be informing the patients honestly about what the role is for prednisone.

Q. Any description here about Dr. de Bono's theory?

A. No.

Q. Any mention of the reversal of resistance of abiraterone that prednisone might be providing?

A. No. All discussions are about safety, mineralocorticoid excess-related, unique toxicities and how prednisone will be

given to these patients to address the side effects.
Q. Okay. So, Doctor, let's recap a little bit. Based on all of the regulatory drug approval documents for Zytiga® that you reviewed, what is your conclusion as to FDA's approval of the use of prednisone when given with Zytiga®?
A. Prednisone has been given to ameliorate side effects associated with Zytiga®'s administration. It has not been approved as an anti-cancer drug.
Q. Okay. And putting yourself back at FDA as a reviewer and assuming that Janssen submitted its Zytiga® NDA and asked for the approval of the same indication, but they also expressly asked that in the approval, FDA specifically acknowledge and approve prednisone for its anti-cancer effects in the combination, would such an NDA have been granted by FDA?
A. No, not at all. I think these were very preliminary, early studies for FDA approval for a new indication, particularly for a drug that -- for a drug that belongs to a pharmaceutical class that are not known as anti-cancer drugs, you know, would require a lot of, a lot of supporting data to get any kind of approval as anti-cancer.
Q. Did the NDA submission even come close to providing that support?
A. No, not at all.
MR. WONG: Let's turn to the approved labeling.
BY MR. WONG:

Q. Doctor, have you reviewed any labeling for the Zytiga® product?
A. Yes, I have.
Q. And which labels -- I know there's a lot of Zytiga® labels floating out there. Which labels have you reviewed in your analysis?
A. I have reviewed Zytiga®'s 2015 and 2018 label -- label.
Q. This has been discussed in court. What is generally the difference between the 2015 Zytiga® label and the 2018 Zytiga® label?
A. So in the 2018 Zytiga® label, it includes the new indication for patients with mCSPC. Also it has -- the clinical studies section had been updated to include trial, LATITUDE trial data.
Q. Now, Doctor, in your opinion, does the 2018 Zytiga® label show that FDA approved prednisone for providing anti-cancer effects when used with Zytiga®?
A. No.
Q. So before you look at the label, can you tell me what the purpose of drug labeling is.
A. The purpose of the drug labeling is the scientific information that is provided on the package insert for the safe and effective use of the drug.
Q. Okay. When approving a label, does FDA make sure that the label contains everything that a doctor would need to safely

and effectively administer the drug?
A. Absolutely, yes.
Q. And does FDA expect doctors to read the entire label?
A. Yes. The regulations require that -- so the labeling has two parts, mainly two parts. It's the highlights and then it has the full prescribing information.
The highlights have selected information from the full prescribing information that healthcare providers consider important while the full prescribing information contains information that is for the safe and effective use of the drug.
Q. And let's look at the Zytiga® label, the 2018 label, DTX 1580. Let's go to the full prescribing information on page 2.
A. Yes.
Q. Let's start with the indications and usage section. Okay.
So, Doctor, what is the indications -- what is described here as the indications and usage for the first mCRPC? Can you read that, please.
THE COURT: We're in 2018, right?
MR. WONG: 2018.
THE COURT: All right.
BY MR. WONG:
Q. Two indications.
A. It says: Zytiga® is indicated in combination with prednisone for the treatment of patients with metastatic

castration-resistant prostate cancer.
Q. And what is the purpose of the indications and usage section in the label?
A. The indication and the usage section is there to -- describes what the drug's indication is, what it's proposed to treat.
Q. Right. And what is the indication -- what is the drug that is the basis for the indication in this Zytiga® label?
A. Zytiga® is the drug. Zytiga® is indicated.
Q. And what does the indications and usage section tell you or tell a doctor about what Zytiga® is indicated for?
A. Zytiga® is indicated for metastatic CRPC and CSPC.
Q. Okay. And what does the indication and usage sections tell you about what prednisone is used for?
A. Zytiga® is used with prednisone. It is taken with prednisone, but prednisone is not indicated for -- as an anti-cancer.
Q. Okay. Is there any other description of the role of prednisone in this indications and usage section?
A. No, not here.
Q. All right. Were you in the courtroom when Ms. O'Shea and Dr. Rettig testified that since prednisone is in the indications and usage section, it means that FDA has approved prednisone for anti-cancer effects to treat prostate cancer patients?

A. Yeah, I was here.
Q. Do you agree with those opinions?
A. No. I disagree.
Q. Why not -- why do you disagree?
A. Well, I think the -- based on the data that I have reviewed in the label, the clinical trial data, the FDA correspondence that I have reviewed, the promotional materials, they all indicate that prednisone is being given to patients to address the side effects associated with Zytiga®'s administration.
Q. You mentioned clinical trials. We'll get to that in the label. But per the regulations, what is the correlation between the indications section and the clinical trial section?
A. The indications section has to be supported by the clinical trial data.
Q. We'll look at that in a second.

So let's look at this -- there was some discussion of the "treatment of patients" language in this indication.

Do you see that?
A. Right.
Q. And what does that mean to you? How does FDA use that language?
A. It's a broad statement. It could mean that patients, the target population for patients who are -- who have CRPC could -- it could mean that patients are -- it's a broad

statement.
Q. Does the use of this statement, treatment of patients, here necessarily mean that prednisone is used for side effects?
A. It could include that as well.
MR. WONG: Let's stay on page 2 and look at the dosage and administration section.
BY MR. WONG:
Q. What is the purpose of this section in the label?
A. This section describes how the -- dosing and dosing regimen for the drug.
Q. Okay. And do you agree with Dr. Rettig and Ms. O'Shea's conclusions that this dosing section somehow confirms that prednisone's dose of 5 milligrams orally twice daily is for anti-cancer use?
A. No.
Q. Why not?
A. Having the statement the recommended dose for metastatic CRPC states: Zytiga® -- Zytiga® is the drug here, and it has to be taken orally with prednisone.
Q. There's no further mention as to any role, specific role of prednisone here in this section, including with respect to anti-cancer effects, right?
A. No.
MR. WONG: Let's go to page 4. Let's look at the warnings and precautions section.

BY MR. WONG:
Q. So what is the role -- why is there this section in a label, a warnings and precautions section?
A. Warning and precautions are potential hazards of the drug.
Q. Okay.
A. And regulations require that they are listed on the label.
Q. Does this section describe anywhere that prednisone has been FDA-approved to treat -- to provide anti-cancer effects at all?
A. No.
Q. Does this section describe the role of prednisone to address side effects of Zytiga®?
A. Yes, it does.
Q. Let's start with section 1. The title is Hypertension Hypokalemia, Fluid Retention Due to Mineralocorticoid Excess.
Right?
A. That's right.
Q. What is described here in 5.1?
A. It says: Zytiga® may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition.
Q. This right here is describing risks that are associated with Zytiga®, right?
A. That's correct.
Q. And specifically, the mineralocorticoid excess risk,

right?
A. That's correct.
MR. WONG: Okay. Let's zoom out a little bit. Let's look at 5.2.
BY MR. WONG:
Q. 5.2 is entitled Adrenocortical Insufficiency.
Do you see that?
A. Yes.
Q. We'll take a look at this, but this section describes what happens when you stop taking prednisone or reduce the role and you take away prednisone, right?
A. That is correct.
Q. But does it also show what the role of prednisone is when treating -- in treating Zytiga® side effects generally?
A. Yes. It says: Adrenal insufficiency occurred in .3 percent of patients taking Zytiga® in comparison to .1 percent of patients taking placebo.
So --
Q. What does that tell you?
A. That tells me that there is more significant population of patients had adrenal insufficiency who were taking Zytiga®.
Q. Okay. Zytiga® might cause adrenal insufficiency?
A. Exactly.
Q. What does the last sentence says?
A. It say: Adrenocortical insufficiency was reported in

patients receiving Zytiga® in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress.

Q. And what does that tell you?

A. That when the steroids are interrupted, you have -- significant patients would get adrenocortical insufficiency.

Q. Does that have anything to do with the role of prednisone in the combination?

A. Yes. When prednisone is given to address, supplement, depleted cortisol.

Q. I think 5.2 carries on to the second page, if you go to page 5 at the top. So what about this paragraph? Does this further confirm the role of prednisone when given with Zytiga®?

A. Yes. It says: Monitor patients for symptoms and signs of adrenocortical insufficiency, particularly if patients have withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress.

Q. What about the last sentence?

A. It says: Increased dosage of corticosteroids may be indicated before, during, and after a stressful situation.

Q. Why is FDA requiring -- what is FDA trying to say here in this language?

A. It says that there is a clear sort of dosing relationship between the side effects and the corticosteroids; that if you have -- under stressful situations, you may require increased

corticosteroids. It's not correlated with its anti-cancer role.

Q. Just to remind the Court, we reviewed some prednisone monotherapy labels yesterday, right?

A. Yes.

Q. Is treating adrenal corticoid insufficiency covered by one of the indications in the prednisone monotherapy label?

A. Yes, it did.

Q. There was a section called Endocrine Disorders, if you recall?

A. Yes.

Q. Would a doctor prescribing Zytiga® with prednisone be expected to review and understand that prednisone is -- that label, the monotherapy label?

A. Yes. I think doctors would be expected to take a look at Zytiga® label as well as the prednisone label.

Q. Right. You've also reviewed the 2015 Zytiga® label, right?

A. Yes.

Q. And you understand -- there was a side-by-side put up yesterday that in the 2015 label compared to the 2018 label in section 5.1, there was a sentence about the co-administration of corticosteroids that was removed in the 2018 label.

Is that your understanding?

A. Yes.

Q. And does whether or not that co-administration section is in an abiraterone label change any of your opinions?
A. No, it doesn't change my opinion just removing a sentence. It doesn't change the basic mechanisms of how Zytiga® and prednisone work.
Q. Right.
MR. WONG: Let's go to page 16, to the clinical pharmacology section.
BY MR. WONG:
Q. Do you see this?
A. Yes.
Q. Let's look at 12.1, specifically mechanism of action. What is described -- what is the purpose of the clinical pharmacology section?
A. So this section actually describes the mechanism of action of the drug pharmacokinetic and pharmacodynamic data as well.
Q. In 12.1, what is described here as to the mechanism of action?
A. It says: Abiraterone acetate is a CYP17 inhibitor.
Q. Does it describe how Janssen thinks Zytiga® will work in the body?
A. Yes, it does describe.
Q. Now, does this section describe anywhere the mechanism of action of prednisone?
A. Yes. In the last sentence of the second paragraph, it

says: Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by adrenals.

And it refers back to the warnings and precautions section.

Q. That's a reference to the side effects treatments of prednisone?

A. Yes.

Q. Does this mechanism of action section in the Zytiga® label describe any other role of prednisone or the mechanism of action of prednisone in providing any anti-cancer effects?

A. No, it doesn't provide any mechanism of action for prednisone.

Q. If the approval of the Zytiga® indication actually approved -- or included a role of prednisone for providing anti-cancer effects with Zytiga®, would there be a mechanism -- would this section look different?

A. Right. At least I think regulations require that there should be either a mechanism of action provided for prednisone. If there is -- the mechanism of action is not known, then at least a statement should be included that the mechanism of action is not known.

Q. To be clear, when we looked at the prednisone labels, there was no mechanism of action that explained any anti-cancer mechanism of prednisone, right?

A. That's correct.

Q. And there wasn't even a statement saying that the mechanism of action of prednisone for anti-cancer effects is not known. That wasn't there either, right?
A. Right.
Q. All right. Let's look, finally, at the clinical studies section.
MR. WONG: Let's go to page 21.
BY MR. WONG:
Q. Again, to orient the Court, you said that there's a correlation between the clinical studies section of the label and the indication?
A. Right. The clinical studies section, the scientific data must support the indication, what is listed in the indications and usage section.
Q. Let's -- how many clinical trials are described here in the 2018 Zytiga® label?
A. Three clinical trials: They are 301, 302, and the LATITUDE trial.
Q. Are these all phase III trials?
A. Yes.
Q. Does the Zytiga® label discuss or include the results of any phase I or phase II studies?
A. No.
Q. And why not?
A. These studies do not form the basis for labeling claims --

efficacy claims on the label, and they are not listed.
Q. Okay. Is there any discussion or even a citation in the label to any scientific articles for Zytiga®?
A. No.
MR. WONG: Let's look at the Cougar 301 study on table 7, page 22.
BY MR. WONG:
Q. So describe this study for us.
A. So the study has basically two arms; the control arm has a placebo with prednisone, and the active arm has Zytiga® with prednisone. It's a -- prednisone is there in both the arms.
Q. Okay. So prednisone is there in both arms, right?
A. Yes.
Q. So, Doctor, based on the description in the label here for the Cougar-301 study, was this study an adequate and well-controlled investigation that could measure the anti-cancer efficacy of Zytiga®?
A. Yes.
Q. How do you know that?
A. Because Zytiga® is there in the active arm, and it's not there in the control arm.
Q. And because Zytiga is an adequate and well-controlled study -- I'm sorry.
Because this study is an adequate and well-controlled study for Zytiga®, does Cougar-301 support the approved

indication for mCRPC patients that Zytiga® is an effective drug to treat prostate cancer?
A. Yes, it does.
Q. All right. And let me ask you the same question for prednisone. Doctor, based on the description in the label here for 301, is 301 an adequate and well-controlled investigation that can measure any anti-cancer effects of prednisone in the combination?
A. No. Prednisone is in both arms. The study is not controlled with respect to prednisone.
Q. All right. And because it's not adequately and well-controlled for prednisone, can Cougar-301 support the approved indication for mCRPC patients that prednisone is an effective drug to treat prostate cancer when given with Zytiga®?
A. Could you restate --
Q. Yeah.
A. -- the question.
Q. Because prednisone is not controlled here.
A. Right.
Q. Does Cougar 301, does this data support the approved indication for mCRPC patients that prednisone is an effective drug to treat prostate cancer patients when given with Zytiga®?
A. No.
Q. So let me ask you this. Is there -- is there -- is there

any substantial evidence of efficacy in the label to show that each of abiraterone and prednisone have anti-cancer effects?
A. No.
Q. And do you recall that during opening arguments the Court asked what kind of study would be needed to prove that both drugs had efficacy in the combination? Do you remember that?
A. Yes.
Q. Well, what would that well-controlled study look like to show that both abiraterone and prednisone had anti-cancer efficacy?
A. I would think that there has to be an additional arm added to the study that would be abiraterone monotherapy arm.
Q. So at least three arms?
A. At least three arms, possibly a fourth arm. But if not possible, at least the three arms should be there.
Q. And so just describe the three arms. Do they include these first two arms?
A. Yes, that --
Q. So one arm would be the combination of Zytiga® with prednisone --
A. Right.
Q. -- right?
One would be the second arm, placebo with prednisone?
A. Right.
Q. And what would the third arm be?

A. It would be Zytiga® plus placebo.
Q. Okay. And what about if you're just trying to tease out any anti-cancer effects of prednisone in the combination, how many arms would you need then? If you just -- yeah. If you just wanted to know if prednisone was contributing?
A. Right. At least you would need two arms.
Q. And what would those arms be?
A. That would be Zytiga® plus prednisone and then you would need Zytiga® plus placebo.
Q. Right. Is there any arm --
THE COURT: Let me just ask. I believe it was suggested that -- suggested or implied that such a study would not be ethical. How does that affect your analysis?
THE WITNESS: I think if the study cannot be carried out, then there has to be additional scientific data would -- should be provided based on -- in either phase II studies or -- I believe additional data would be needed; I cannot think of right now.
THE COURT: Thank you.
BY MR. WONG:
Q. In the absence of another control arm that had -- just had abiraterone monotherapy and placebo, did you see any data in the NDA filing that would have substituted for that information?
A. Can you restate your question.

Q. All right. You said that what you would need -- what Janssen would have needed to do was to conduct another trial that had another arm with just abiraterone monotherapy and placebo, right?
A. Right.
Q. And for ethical reasons if that couldn't be done, was there any other information that was submitted in the NDA filing that could have substituted for that arm that would have allowed FDA to approve the combination where both drugs have anti-cancer efficacy?
A. No. No other data was submitted.
Q. Thank you.
All right. That's for 301, right?
A. Right.
Q. And then there's a 302 study, table 8, page 23, right?
And I won't go through the same questions, but is the 302 study of similar design to the 301 study?
A. Yes, the basic design, trial design, stays the same.
Q. And those -- are your opinions as to the adequacy of this trial the same with respect to supporting anti-cancer effects of each of abiraterone and prednisone?
Are your opinions the same --
A. Yes.
Q. -- as to the 302 trial as they relate to the 301 trial?
A. Yes.

Q. All right. Let's look at the third clinical trial, the LATITUDE study. That's on page 26, table 10. What is the trial design of the LATITUDE study?
A. So the LATITUDE trial design has two arms; one arm is the placebo and the other arm, the active arm is the Zytiga® with prednisone. And I think both arms also have ADT.
Q. Was the LATITUDE -- and to be clear, the LATITUDE study is not in any of defendants' labels, right?
A. No, they're not. It's not.
Q. Okay. And is the LATITUDE study adequate and well-controlled to measure any anti-cancer efficacy of prednisone in the active arm?
A. No.
Q. And why not?
A. You cannot parse out the effect of prednisone in this study.

Zytiga® -- so Zytiga® is the drug here and Zytiga®'s -- this is a supplemental NDA. Zytiga® has been proven to be anti-cancer in the previous two trials. And so this study is controlled for Zytiga® but you cannot parse out the role of prednisone in this trial as well.

Q. Okay. So we've reviewed the three clinical trials in the Zytiga® 2018 label.

Since -- I think you've testified to this, but since none of the phase III trials are adequate and well-controlled

to measure prednisone's efficacy -- any anti-cancer efficacy of prednisone, what does that mean in terms of the indications section, of FDA's approval of prednisone in the indications section?

A. Well, the trial data, scientific data does not support that prednisone has any anti-cancer role. It's not -- and so in the indications and usage section Zytiga®'s listing is supported by the scientific and clinical trial data; but prednisone's listing as anti-cancer, that is not supported.

Q. So let's go to page 30, and let's look at the patient information section. So what is the purpose of this patient information section at the back of the label?

A. This is part of the label that has the less formal language. The purpose is to inform the patients, you know, how the drug works and how they should take the drug --

Q. Okay. So just like the informed consent, it's written at kind of a more plain English --

A. Yes.

Q. -- language?

A. Right.

Q. All right. Let's take a look at the top, there's a section -- the first section says: What is Zytiga®?

Do you see that?

A. Yes.

Q. And what does the patient information section explain here

to patients?
A. It says: Zytiga® is a prescription medicine that is used along with prednisone.
I think it clarifies here how the Zytiga® is used.
Q. Okay. What does it go on to say about Zytiga®?
A. Zytiga® is used to treat men with prostate cancer that has spread to other parts of the body.
Q. So in terms of treating the cancer, what is conveyed here to -- what is FDA conveying here to patients?
A. It states: Zytiga® is a prescription medicine that is used along with prednisone.
So Zytiga® is the drug.
Q. And does this -- is this section consistent with the previous section, which is targeted to doctors, as far as the approved indication of Zytiga®?
A. Yes.
Q. All right. So let's recap on this label.
Just based on what is in the label that we've just reviewed, what is your opinion as to whether prednisone is approved for anti-cancer effects in the combination with Zytiga®?
A. FDA has not approved prednisone as an anti-cancer when it is given as part -- as -- with Zytiga®.
Q. And is that consistent with what you've seen in the administrative record, the FDA approval record leading up to

Zytiga®'s approval?
A. Yes.
Q. Okay. Let's talk about -- you were here for the discussion over the last couple days about the marketing materials, how Janssen markets Zytiga®?
A. Yes.
Q. And have you yourself reviewed any of Janssen's marketing materials related to Zytiga®?
A. Yes, I have.
Q. Are marketing materials submitted to FDA for approval?
A. After the approval of the NDA is granted, the marketing materials, they are submitted to the FDA.
Q. They don't need pre-approval?
A. They don't need pre-approval.
Q. But they do need to be approved by FDA; is that right?
A. Right.
Q. Let me ask you this, can a drug company market -- strike that.

Does FDA allow a drug company to market an unapproved use of a drug?
A. No.
Q. Okay. And what are the consequences for a company to market a product for an unapproved use?
A. There could be enforcement actions from the FDA that could potentially violate a misbranding provision of the FTC Act, so

I think there could be some legal repercussions.

Q. Okay. So I think we've seen --

THE COURT: Let me just back up for one second.

We all know that off-label promotion can get you in a world of trouble. That's not disputed. What I'm looking at, though, is whether it's really black and white. I guess there was earlier testimony saying that, yes, in general that's the principal; but I mean just anecdotally it occurs to me I have seen advertisements, including one that looks like playing with dynamite where someone -- some medication they said, well, it's not approved for this but, you know, you could lose weight. We can all see the problem.

But tell me, is it really so black and white that you cannot promote any -- obviously you cannot represent an off-label use as an on-label use, but is it really true you cannot at all promote an off-label use in your marketing materials?

THE WITNESS: Your Honor, regulations require that you cannot promote the off-label use. But FDA's resources are limited. They cannot enforce every off-label use. And so there are -- you know, you see these kind of violations, so to speak.

THE COURT: Okay. So I'm just getting at the premise of your opinion here which is that, okay, if it's off-label, you can't have it in your marketing?

THE WITNESS: Right.
THE COURT: That's your premise, okay. Go ahead.
MR. WONG: Thank you.
BY MR. WONG:
Q. So let's take a look at some other documents. We're not going to pull up all the documents. I think they've been discussed already in court, but let's see DTX 1274.
You were in court when this was discussed, right, Doctor?
A. Yes.
Q. And this is entitled Putting Prednisone in Perspective, right?
A. Yes, it's the promotional material from Janssen, it says Putting Prednisone in Perspective --
Q. Okay.
A. -- Understanding the Role of Prednisone in Combination with Zytiga®.
Q. Right. And you've -- you've relied on this to form your opinions in this case, right?
A. Yes.
Q. Let's just pull up another one really quickly, DTX 1260.
I think we've also seen this document in court?
A. Yes.
Q. Can you just read the title.
A. It says: Prednisone reduces the incidence of severity of

mineralocorticoid-related adverse reactions with Zytiga®.
Q. And have you also relied on this document in forming your opinions?
A. Yes.
Q. Let's take a look at the third one, DTX 1273. I think this was from the FDA -- I'm sorry, the Zytiga®.com website. Do you remember this?
A. Yes.
Q. And did you also rely on this document in forming your opinions in this case?
A. Yes.
MR. WONG: We can put all three of them on the screen.
BY MR. WONG:
Q. So in general what is described -- what is Janssen telling the public here in each of these three marketing materials for its Zytiga® product?
A. Janssen is telling that Zytiga® is there to address the side effects of mineralocorticoid excess due to Zytiga®'s administration -- the prednisone is there to address the side effects.
Q. Okay.
A. There is no mention of prednisone having any kind of anti-cancer role with Zytiga®.
Q. Is there any mention in any of these three documents that

prednisone -- of -- of Dr. de Bono's hypothesis that prednisone is somehow reversing the resistance of abiraterone due to the promiscuous AR?

A. No, there is no mention of any such hypothesis.

Q. Right. And especially in the Putting Prednisone in Perspective, that first document, Understanding the Role of abiraterone -- Prednisone in the Combination, right?

There's no -- is there any description in that document?

A. Not at all. I think you would expect that Janssen explain clearly, you know, how prednisone works in combination with Zytiga®, at least in this document.

Q. And in any documents that you reviewed on promoting Zytiga® has Dr. de Bono's theory even been suggested or described?

A. No, I have not seen any of the FDA documents, any of the FDA records that talks about Dr. de Bono's hypothesis.

Q. Right. And the promotional -- including the promotional materials?

A. Promotional materials.

Q. I believe there are a couple other promotional materials that were used with Ms. O'Shea.

MR. WONG: Can we put those up. Those were PTX 424 and 447. I'll put them side by side.

BY MR. WONG:

Q. Just briefly, were you in the room when Ms. O'Shea reviewed these -- when counsel put these in front of Ms. O'Shea?
A. Yes.
Q. And do these documents at all change your opinions on how Janssen markets the role of prednisone to the public?
A. No.
Q. Why not?
A. I think we have put the indications here: Zytiga® plus prednisone achieved statistically significant median overall survival difference.

It doesn't change my opinion.

MR. WONG: Okay. And for the record, I think I might have said PTX 427. I meant 447, which is up on the screen now. I apologize.

BY MR. WONG:
Q. Okay. And do either of these -- so it just -- it describes the 301 study, is that what you're saying?
A. That's right.
Q. Right. Does it -- do either of these tell the public that prednisone is providing an anti-cancer effect in the combination?
A. No.
Q. Do any of these describe or even allude to Dr. de Bono's hypothesis theory?

A. No, not at all.
Q. All right. Let's -- let's talk about -- let's try to wrap up. Let's talk about the materials we've reviewed so far. So we've reviewed the -- so let me ask you this.
What type of materials have we reviewed so far that help form your opinions?
A. I have reviewed Zytiga®'s labels or labeling, package inserts. I've reviewed FDA correspondence, FDA records. I've reviewed the clinical trial data, the NDA and SNDA documents from Janssen. I have reviewed the promotional material.
Q. Okay. And did you also review each of defendants' labels in this case?
A. Yes, I have reviewed.
Q. And how -- generally speaking, how do defendants' labels compare to the Zytiga® 2018 label?
A. Defendants, they have carved out the indication for mCRPC alone. They have -- they don't have LATITUDE clinical trial data. Otherwise they are similar.
Q. Any -- besides those two differences, are there any other substantive differences between each of defendants' labels and the 2018 Zytiga® label?
A. No.
MR. WONG: Okay. Now let's go to the next slide.
BY MR. WONG:
Q. All right. So given that defendants -- each of

defendants' carved-out labels are substantively identical to the 2018 Zytiga® label, what is your opinion as to whether defendants' labels induce infringement of the asserted claims?

A. Defendants' labels do not induce the asserted infringement of the '438 patent.

Q. And why is that?

A. The '438 patent claims require that both abiraterone and prednisone each provide anti-cancer efficacy. And based on my review, FDA has approved only Zytiga®, not prednisone, for anti-cancer efficacy.

Q. Let's go to the next slide and talk about your opinions as to contributory infringement. What is your opinion as to whether each of defendants' carved-out labels will contribute to infringement of the asserted claims?

A. They do not contribute to the infringement.

Q. And why is that?

A. Defendants are seeking approval only for the FDA-approved use of abiraterone in combination with prednisone for safety not anti-cancer efficacy.

And '438 patent claims require using prednisone with abiraterone for anti-cancer efficacy; therefore, FDA-only approved use is also a non-infringing use.

MR. WONG: No further questions. I pass the witness.

THE COURT: All right. Before I proceed, this might be a good time, given the schedule today, to take a morning

break. So let's reconvene in 15 minutes. Okay?

MR. WONG: Thank you.

(Break taken 10:40 a.m. through 10:55 a.m.)

THE COURT: Everybody ready? Let's continue.

MR. REIN: Your Honor, before I begin cross --

THE COURT: Sure.

MR. REIN: -- can I read the exhibits?

THE COURT: Just as good a time as any. Sure.

MR. REIN: The exhibits that should be admissible from yesterday -- and we've run this by defendants as well -- are the following: PTX -- they're all PTX.

I will just read the numbers:

22, 31, 148, 154, 344, 424, 447, 450, 451, 452, 453, 454, 455, 456, and 457.

THE COURT: Okay. No objection, I take it?

MR. WHITE: Your Honor, we do have an objection to 450 to 457 coming in as evidence.

THE COURT: Remind me what they were.

MR. WHITE: They are claim terms that Dr. Rettig briefly mentioned that he prepared, although we didn't go through them in detail. We are fine if they come in as demonstrative. We don't think they should come in as evidence.

MR. REIN: Your Honor, our position is that they're summary reports pursuant to Federal Rule of Evidence 1006. Obviously, Your Honor will give whatever weight to them

Your Honor believes is appropriate. We do think it's evidence. And, in fact, they did not object to it last night or the night before.

THE COURT: That's okay. I understand the objection. I hear it.

Listen, I will use them as appropriate. Again, there's no jury that has to be protected from undue influence here. I know what they are. I know what charts are, and I will use them appropriately.

Okay?

But subject to that, the list of exhibits is admitted.

(PTX Exhibits 22, 31, 148, 154, 344, 424, 447, 450, 451, 452, 453, 454, 455, 456, and 457 received in evidence.)

MR. REIN: Thank you, Your Honor.

Just as a last housekeeping matter for the court reporter's convenience, I will hand her the list.

THE COURT: Yes.

At this point I know who you are, obviously. But for the record, introduce yourself.

MR. REIN: I will indeed. In fact, I will introduce myself to the witness as well since we haven't met.

(CROSS-EXAMINATION)

BY MR. REIN:

Q. My name is Thomas Rein from the law firm Sidley Austin.

Good afternoon, Dr. Nagaich.
A. Good afternoon.
Q. Dr. Nagaich, you are not a lawyer, correct?
A. That's correct.
Q. You haven't read the case law on what is required for induced infringement or contributory infringement in a Hatch-Waxman case, correct?
A. That is correct.
Q. You're relying on defendants' lawyers with regard to what is required to be in the label, correct?
A. What is --
Q. From a legal standpoint?
A. From the legal standpoint, yes.
Q. And defendants' lawyers specifically told you that the labels here must specifically indicate that prednisone in the combination provides an anti-cancer effect, correct?
A. That is the claim construction, Court's claim construction that I interpreted that way.
Q. But the defendants' lawyers told you that the label must specifically call out that anti-cancer benefit for prednisone, correct?
A. Yes.
Q. And it's your view that because the label does not do that, there is no induced infringement or contributory infringement, correct?

A. That is correct.
Q. That's the sole basis for your opinion on non-infringement, correct?
A. Correct.
Q. If the Court concludes that the label merely needs to disclose the same two drugs, abiraterone and prednisone, in the same amounts, 1000 milligrams per day for abiraterone and 10 milligrams per day for prednisone, to treat the same disease, if the Court concludes that that's all the label has to say, then your conclusions on infringement are legally irrelevant, correct?
A. I am not a lawyer. And, you know, I don't understand the legal language for it. I have reviewed these -- I understand the patent. I have reviewed the patent. I have reviewed the FDA label, approved label, and --
Q. That's not answering my question, sir.
If the Court concludes that all the label needs to do is identify the same drugs, abiraterone and prednisone, in the same amounts that are set forth in the claims to treat the same disease, then your opinions on infringement are legally irrelevant, true?
A. You're asking me whether they're legally relevant or irrelevant?
Q. Your analysis is beside the point if the Court concludes that the label doesn't have to specifically identify prednisone

as having an anti-cancer effect, correct?
A. I'm sorry. I'm not understanding your question, sir.
Q. If the Court concludes --
A. Uh-huh.
Q. -- that the label --
A. Yes.
Q. -- simply needs to call out the same drugs in the same amounts that are set forth in the patent claims for the treatment of prostate cancer, then your opinions on infringement are all beside the point, correct?
A. I'm -- my -- I'm not understanding, sir, your question. I apologize to you.
Q. Let me try it this way. If --
A. Okay. Good.
THE COURT: Could the problem be this, that you're saying "the label needs to"?
MR. REIN: Yes.
THE COURT: That could be from any number of points of view, some of which are within his expertise, some of which are not. Maybe you can clarify that.
MR. REIN: Let me try it this way.
BY MR. REIN:
Q. If the Court concludes that a label is sufficient to induce infringement or to lead to contributory infringement, if it calls out the same drugs in the claims, prednisone and

abiraterone acetate, in the same amounts recited in the claims, 10 milligrams per day for prednisone, 1000 milligrams per day for abiraterone acetate, and that those drugs need to be indicated to be for the treatment of prostate cancer, if that's, according to the judge, as a matter of law all the label needs to say for infringement, then your opinions on infringement are beside the point, true?

A. Right.

Q. And by the same token, if the Court concludes that all the label needs to do is call out the same drug and the same amounts for the treatment of prostate cancer so long as the prednisone ends up having an anti-cancer effect, then again, your opinions about contributory infringement and inducement are beside the point, correct?

A. Correct me --

Q. Pardon me?

A. I'm not understanding your question, sir.

Q. The same question as the last time --

A. Yeah.

Q. -- but this time the additional element is: If the Court concludes that the label also has to be such that the prednisone -- strike that. Let me try it again. I'll ask the question again.

If the Court concludes that the label is sufficient to induce or cause contributory infringement if it identifies

10 milligrams per day of prednisone, 1000 milligrams a day of abiraterone to treat cancer, so long as the prednisone and the abiraterone both have anti-cancer effects but that doesn't have to be said on the label, then your opinions are beside the point, correct?

A. As I understand the label in the Court's constructed claim, both the prednisone and abiraterone acetate have to have anti-cancer effect.

Q. I understand that. My point is: If the Court finds, as a matter of fact, that the abiraterone in that amount has an anti-cancer effect and that the label doesn't have to specifically say that; it just has to prescribe the 10 milligrams of prednisone and that prednisone has to have that anti-cancer effect, then your opinions about the label are beside the point, true?

A. No. Actually, the label has to say that.

Q. The reason why you're saying the label has to say that is because defendants' counsel told you the label has to say that, correct?

A. No, in my -- as an FDA labeling expert, the label has to say that, that prednisone has an anti-cancer effect.

Q. From a Hatch-Waxman standpoint, are you saying that the label has to specifically call out that prednisone has an anti-cancer effect? Is that what the case law says?

A. I'm not a lawyer. I don't understand the case law.

I understand that the label has to specifically call out that prednisone has an anti-cancer effect.
Q. Is there a regulation, FDA regulation you can call to my attention that says prednisone when it's in a label has to have an anti-cancer effect?
A. If Janssen is proposing that this is -- prednisone is indicated for cancer, mCRPC, then there has to be -- it has to be on the label. It has to have scientific data to support that.
Q. That's not my question. My question is --
THE COURT: Would it help if I told you I understand the distinction you're drawing?
MR. REIN: Yes.
THE COURT: There's legal matters. There's Hatch-Waxman matters. There's matters of regulatory requirements. And they're not the same thing.
MR. REIN: Very well.
THE COURT: He's expert in one, not in the other.
BY MR. REIN:
Q. So let me ask you this --
THE COURT: Excuse me just one moment.
Go ahead.
BY MR. REIN:
Q. Are you saying, Dr. Nagaich, that the reason you think the label must indicate that prednisone has an anti-cancer effect

is the reason because otherwise there would be an off-label use?
A. Yes. It would be an off-label use if prednisone is not indicated for anti-cancer.
Q. And is that the reason why you say that the label must spell out that prednisone has an anti-cancer effect that otherwise it would be an off-label use?
A. There has to be data supporting prednisone's role as an anti-cancer.
Q. Data where? In the indications and usage section?
A. Clinical trial studies should support the indications and usage section.
Q. You did testify about off-label use.

I'm asking you: Is the reason why you think the label has to specifically call out prednisone's anti-cancer effect that, otherwise, it's an off-label use in the FDA's parlance?
A. Could you restate your question, sir.
Q. What's the significance of whether or not it's an on-label or off-label use, sir? Does that have anything to do with the infringement case, the infringement issue in this case?
A. If the label is -- if the FDA-approved use is an off-label use, then there is no infringement.
Q. So you're saying what's important from a FDA regulatory standpoint is whether the label is instructing an off-label or

an on-label use; is that your testimony?

THE COURT: Wait. The label is instructing an off-label use?

MR. REIN: A fair observation.

BY MR. REIN:

Q. Let me ask you this: Would you agree with me that, that there simply is no established definition of the term "off-label use" in FDA's regulations?

A. There is no established definition for "off-label use." But off-label use is FDA unapproved use, is an off-label use.

Q. But there's no FDA-established definition, true?

A. That is correct.

Q. Now, returning to what you were advised by counsel that is necessary in order to meet the claims and have infringement, what you were specifically told by counsel, as stated in your expert report, is that Zytiga®'s labeling must teach that prednisone be specifically administered in an amount effective for treating cancer, correct?

A. Yes. Correct.

MR. REIN: And did we put -- well, let me -- could we put claim 1 on the screen, please, JTX 8000.

BY MR. REIN:

Q. That's claim 1, and that contains the language "therapeutically effective amount," correct?

A. Yes; therapeutically effective amount of abiraterone

acetate and therapeutically effective amount of prednisone.

MR. REIN: Can we turn, Matt, to claim 8, please.

BY MR. REIN:

Q. Claim 8 specifically says that the therapeutically effective amount of prednisone is about 10 milligrams per day, correct?

A. Yes, it says that. Yes.

Q. You aren't able to tell us whether someone would practice the claimed method of the '438 patent if they administered to a human with prostate cancer a therapeutically effective amount of abiraterone acetate and a therapeutically effective amount of prednisone, correct?

A. The therapeutically effective amount of prednisone should be to treat prostate cancer.

Q. I'm asking you: Are you able to tell us whether someone would practice the claimed method of the '438 patent if they administered to a human with prostate cancer a therapeutically effective amount of abiraterone acetate and a therapeutically effective amount of prednisone? Can you tell us that, sir?

A. I am not a patent lawyer. I cannot --

Q. You can't answer that question?

A. I can't answer that question.

Q. You have no opinion on that, correct?

A. I have no opinion on that. I cannot answer your question.

Q. And so you can't tell us whether clinicians will infringe,

directly infringe these claims, correct?
A. I understand that if the independent claim is not infringed -- I have focused my analysis on the claim 1. And if that claim is not infringed, then all the dependent claims will also not be infringed.
Q. That's not my question.
I think you just told us a minute ago you don't have an opinion on direct infringement, isn't that true, because you're not a lawyer?
A. I'm not offering my opinion on direct infringement.
Q. All right. Let me also cover a few background matters.
Just so the record's clear, you are not a physician, correct?
A. That is correct.
Q. You do not have an M.D. degree, correct?
A. That's correct.
Q. You have no training in the field of medicine at all, correct?
A. That's correct.
Q. You've never provided medical treatment to a cancer patient, of course, correct?
A. That's correct.
Q. You're not an expert in prostate cancer treatment, correct?
A. That is correct.

Q. You have no skills in oncology, correct? That's not your area of expertise?
A. It depends how you define "oncology" as a scope. I have been a cancer researcher for almost 13 years. So it's very broad term.
Q. In any case, you're not an expert in prostate cancer treatment, correct?
A. Not the treatment, yes. I'm not.
Q. And you're not a person of ordinary skill in the art to which this patent is directed, correct?
A. That is correct.
Q. You're simply looking at the information from an FDA point of view, true?
A. That is true.
Q. Now let's talk about your tenure at FDA. When you worked at FDA, you worked in the office of biotechnology products of the Center for Drug Evaluation, correct?
A. That is correct.
Q. And the office of biotechnology products is not responsible for the review and approval of drug applications on small chemical compounds like abiraterone acetate and prednisone, correct?
A. Generally, that is correct. Office of biotechnology products review the biologies.
Q. You yourself did not work in the office of oncology

products at FDA, correct?
A. I did not work in that office.
Q. And FDA's office of oncology products, not the office of biotechnology products, is who signed off on the approval of Zytiga®, correct?
A. That is correct.
Q. Let's talk about labeling. It's true, isn't it, that the FDA expects that healthcare practitioners will follow approved labeling when prescribing a prescription drug?
A. That is correct.
Q. And here you are offering opinions on behalf of the defendants, the generic companies, correct?
A. Yes.
Q. Defendants understand, based on FDA requirements, that when their ANDAs are approved, their abiraterone will be prescribed and used according to the proposed ANDA product labeling, correct?
A. I -- did you say "defendants understand"?
Q. Yes.
A. Well, I think the FDA -- the -- it is FDA's expectations that physicians and healthcare providers will use the drug as -- in accordance with the approved label. I cannot speak to what the defendants expect or what they think.
Q. Well, you are consulting on behalf of the defendants, right?

A. I have looked at their data from the FDA point of view, as an FDA labeling expert, and analyzed that.
Q. You remember having your deposition taken in this case?
A. Yes.
Q. Do you have your transcript in front of you?
A. I don't have a transcript in front of me.
Q. Let me hand you one.
MR. WONG: Could I get a copy?
Can I get a copy of the transcript?
MR. REIN: Yes, you can.
THE COURT: Help me out. Is this the same thing I have in my black notebook?
MR. REIN: You know, the defendants passed up the depositions. I'm not sure what --
THE COURT: I was actually asking the defendants.
I have something called 2017 deposition and 2018.
MR. WONG: Can I get a copy of this transcript that you are going to cross him on?
MR. REIN: You have the transcript --
THE COURT: I'm asking if it's the same thing.
MR. REIN: Yes, it is. I'm having to provide it to defendants.
THE COURT: Okay. We have a 2017 dep. We have a 2018 dep.
MR. REIN: Correct.

THE COURT: Which one is it?

MR. REIN: This one in particular that I'm going to direct his attention to is the July 19, 2017 deposition.

THE COURT: Which is the second or third -- or actually third item in the black notebook --

MR. WONG: Okay.

THE COURT: -- that you guys handed up. Okay.

BY MR. REIN:

Q. Could you turn to page -- first of all, let me ask, you do recall having your deposition taken twice in this case, right?

A. Yes.

Q. And you were sworn to tell the truth?

A. Yes.

Q. Just like you were sworn to tell the truth today, right?

A. Yes.

Q. So you did tell the truth to the best of your ability, correct?

A. That is correct.

Q. All right. So why don't you take a look at page 80, starting at line 22, where you were asked the following question and did you give the following answer?

"QUESTION: When the ANDA is approved, it is defendants' general understanding that the drug will be used and will be prescribed according to their proposed ANDA product labeling, correct?

"ANSWER: That is correct."

Did you give that answer to that question, sir?

A. Can I just take a second to review?

Yes, I said that.

Q. All right. So let's now walk through some of the different portions of the product labels. And to save us time, the Zytiga® label and the defendants' proposed labels, they're all substantially the same, correct?

A. Yes.

Q. So let's start with the indications and usage portion of the labeling.

Would you agree with me that this is a critical subsection of the label?

A. Yes. It's an important subsection of the label.

Q. It's a critical subsection, correct?

A. Which section are you talking about?

Q. The indications and usage portion of the labeling.

A. In the highlights or for the prescribing information?

Q. In both collectively. It's -- they're critical --

THE COURT: Tell us the number of the section. That may help.

THE WITNESS: It's a -- it's a -- yes, it's an important --

BY MR. REIN:

Q. I'm actually asking you if it's critical, if that is a

critically important section, yes or no?
A. Yes, I could say critically important section, yeah.
Q. And the purpose of the indications and usage section is to state the specific disease or condition for which the drug or drugs are approved, correct?
A. Yes.
Q. The indications and usage portion identifies the drug as well as what it purports to cure or is supposed to do, true?
A. True.
MR. REIN: All right. Can we put up PTX 408, page 2 please.
I'm sorry. I think it's 406. If we could blow up the indications and usage section, please.
THE COURT: For the record, the 2018 label, right?
MR. REIN: I believe that's right. Yes.
BY MR. REIN:
Q. This is the indications and usage section from the 2018 Zytiga® label, correct?
A. That is correct.
Q. And for the Zytiga® label as well as the defendants' labels, the indications and usage section recites only -- well, let me step back.
In -- the defendants' labels do not have the second indicated condition, metastatic high-risk castration-sensitive prostate cancer, correct?

A. That's correct.
Q. They only have the first one, correct?
A. Yes.
Q. So the defendants' labels only identify a single disease, metastatic castration-resistant prostate cancer, correct?
A. Yes.
Q. And so the indication that's set forth in their label is to treat metastatic castration-resistant prostate cancer, correct?
A. That is correct.
Q. That's the disease to be treated, true?
A. Yes.
Q. And the only drugs that are mentioned in this portion of the label are abiraterone acetate and prednisone, correct?
A. Zytiga® is the drug that that treats the metastatic prostate cancer.
Q. I'm sorry. This label specifically says Zytiga® is indicated in combination with prednisone, correct?
A. It says that, but if I am going --
Q. My question is: Does it say that Zytiga® is indicated in combination with prednisone, yes or no?
A. It says Zytiga® is indicated in combination with prednisone; but as I said before, Zytiga® is indicated for -- to treat the mCRPC.
Q. You're having trouble with my question.

The label does say that Zytiga® is indicated in combination with prednisone, correct?
A. Yes. As I read it, yes. Uh-huh.
Q. And the defendants' labels say that abiraterone acetate is indicated in combination with prednisone, correct?
A. That is correct.
Q. The indications and usage sections of defendants' ANDA labels do not identify any use for the combination of abiraterone acetate and prednisone other than the treatment of patients with metastatic castration-resistant prostate cancer, correct?
A. That is correct.
Q. And as for whether the FDA draws a distinction between treating a patient who suffers from -- let me start the question again. I stumbled twice.

As for whether the FDA draws a distinction between treating a patient who suffers from a disease and treatment of the disease itself, you have no opinion on that, correct?
A. I have no -- I mean, I have -- treating a disease or treating a patient with the disease, I think treatment of patients could include treating the disease itself or -- and it's a very broad term. It could include treating the disease and the side effects as well.
Q. Do you have your deposition?

Why don't you turn to your July 19 deposition once

again, sir. I'd like you to focus on your testimony at page 158. Specifically, I'm going to start reading at line 22.

A. You said which page?

Q. And let's start on line 24.

A. Of page number which? Which page?

Q. 158. The question that you were asked --

THE COURT: Wait a second.

Have you got that?

THE WITNESS: Yeah. 158, line number 22?

BY MR. REIN:

Q. Twenty-four, sir.

A. Twenty-four. Okay.

Q. The question that you're asked -- that you were asked was the following: The FDA does not draw a distinction between treating a patient who suffers from disease and treatment of the disease itself because approval is based on whether the treatment is effective to treat the disorder itself.

Do you agree with that opinion?

And your answer was: I -- I have -- I haven't thought about this, this particular sentence, and I cannot offer you my opinion on this.

That was your testimony at your deposition, correct?

A. That is correct.

Q. Now, the indications and usage section does not mention the word "side effects" or "managing side effects," true?

A. True.
Q. And under FDA regulations, indications or uses must not be implied or suggested in other sections of the labeling if not expressly included in the indications of use itself, right?
A. That is correct.
Q. There are not, in essence, two indications in the defendants' labels, one addressing the metastatic castration-resistant cancer and another one described as addressing side effects, correct?
A. Side effects is not a disease. So it is correct that there are not two indications. As I said before, the prednisone is being given to address the side effects of Zytiga®.
Q. Let's try my question.
There's only a single indicated condition, and that's prostate cancer, correct?
A. That is correct.
Q. And the indications and usage section does not even mention the words "side effects," correct?
A. The side effects are not generally mentioned in the indications and usage section.
Q. Are you saying it can't be? Never is?
A. I have not analyzed all the labels. But in my experience, generally, side effects are not mentioned in the label, but it could be.

Q. Yesterday you identified the prednisone label, JTX 8125, during your direct examination, and you pointed to the indications section of that label.

MR. REIN: Could we pull that up.

BY MR. REIN:

Q. And I believe you said that the indications section specifically called out neoplastic diseases?

A. Yes.

Q. And the neoplastic diseases indication says: For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood.

Correct?

A. That is correct.

Q. So it specifically identifies palliation in the indications of use, correct?

A. Yes. It says: Palliative management.

Q. So if prednisone were for palliation in the abiraterone labels, it could have called out that palliation function in the label itself, correct?

A. Not necessarily.

Q. But it could have, right?

A. It depends. I think you are talking about two different -- this is the well-known use for glucocorticoid receptors. And in this label, what you see, that glucocorticoids or prednisone is being used for palliative

management of leukemias and lymphomas.
Q. Now, if I am reading this correctly, it does not say that this prednisone product is indicated for the palliation of prostate cancer. There's no mention of prostate cancer there, right?
A. That is right. There is no mention of prostate cancer. It's there for palliative management of these other neoplastic diseases.
Q. So would it be your position that using prednisone for palliation in connection with the treatment of prostate cancer would be an off-label use?
A. Could you please restate your question.
Q. My question is: If a doctor employed this prednisone product for palliation in connection with a prostate cancer treatment, would that be an off-label use?
A. No. This would -- that won't be off-label use.
Q. Even though prostate cancer is not mentioned here?
A. Did you -- I'm sorry. Did you say if -- if the doctor prescribes this for the palliation of prostate cancer?
Q. Would it be off-label?
A. Would it be off-label use for --
Q. Yes.
A. -- prednisone?
Q. Yes.
A. It could be considered off-label use, uh-huh.

Q. If I heard you correctly yesterday, based on your review of the prednisone labels, you concluded that FDA never approved prednisone as a monotherapy as an anti-cancer treatment.

Did I take that down correctly?

A. That is -- yeah, that is correct.

Q. And I think you said today that they've never approved prednisone for an anti-cancer use; is that right?

A. That is correct.

Q. And did you say you reached that conclusion because you reviewed all the available package inserts for prednisone and have not seen any indications as an anti-cancer agent for prednisone?

A. Yes.

Q. That's what you looked at, were the labels?

A. Yes.

Q. And you didn't review FDA approval packages for prednisone, did you?

A. I reviewed all the approved -- FDA -- you said FDA approval packages or package inserts?

Q. Did you review the FDA approval packages, the entire packages for prednisone?

A. I reviewed whatever were available, but not all the approval packages are available.

Q. So you reached your opinion about prednisone without reviewing or looking at the FDA approval packages, true?

A. I reviewed all the information, including package inserts, approval packages, that are available, publicly available.
Q. Did you review all the package -- I'm sorry -- all the FDA approval packages for prednisone in connection with your testimony today? Yes or no.
A. I did review.
Q. You reviewed all the -- I'm asking you whether you reviewed all of the FDA approval packages for prednisone in connection with your testimony. Yes or no?
A. I reviewed whatever is available on the publicly available -- public websites and the FDA website, all the information.
Q. What percentage of the approval packages for the prednisone products did you review? How many were available -- one? Two? How many?
A. Like I said, I reviewed the FDA labeling information.
Q. I'm asking about approval packages.

There's a difference between a label and an FDA approval package, correct?
A. Like I said, approval packages are not available for a lot of these products that I listed.
Q. That's what I'm getting at. You didn't review them, did you?
A. No, I did not.
Q. And you didn't review any INDs for prednisone, did you?

A. No, I did not.
Q. And you didn't review any NDAs for prednisone, did you?
A. No, I did not.
Q. And you didn't review any promotional materials for prednisone, did you?
A. That is correct. I did not review promotional material. That's right.
Q. And you did not review any FDA decisional memos for prednisone, correct?
A. I did not review. That's correct.
Q. All right. Let's move to the dosage and administration section on Plaintiffs' Exhibit 408. And, again, we're on the 2018 Zytiga® label, correct?
A. That is correct.
Q. Would you agree with me that together, the instructions and usage and dosage and administration sections of defendants' ANDA labels -- I'm being corrected.

This is Plaintiffs' Exhibit 406, not 408, for the record. So let me withdraw the question and start it again.

Together the indications and usage, and dosage, administration sections of defendants' ANDA labels instruct the use of 1000 milligrams of abiraterone acetate and 5 milligrams of prednisone twice daily to treat patients with metastatic castration-resistant prostate cancer.

Correct?

A. That is correct.
Q. And those are the same drugs and amounts as what is recited in the '438 patent claims, correct?
A. Yes. Correct.
Q. And the labels also call for co-administration of prednisone with Zytiga®, correct?
A. Only two of the defendants' labels call for that co-administration.
Q. Only two of the labels use the language "co-administration"?
A. Yes, right.
Q. But they all call for abiraterone acetate in combination with prednisone, correct?
A. That's right.
Q. And functionally the labels all mean the same thing, correct?
A. That is correct.
Q. And so people following defendants' ANDA labels will administer 1000 milligrams per day of abiraterone acetate and 5 milligrams of prednisone twice a day for metastatic castration prostate -- or metastatic castration-resistant prostate cancer, correct?
A. Correct.
Q. Let's briefly talk about the warnings section. And you are aware that -- well, let me start with a foundational

question.

Is it true that the FDA would give careful consideration to what is included in the Zytiga® product label?

A. Yes.

Q. And you understand that the FDA agreed that Janssen could remove the sentence that deals with the co-administration of corticosteroids, correct?

A. Yeah. That's -- that sentence was removed. Whether FDA agreed, I do not know. I cannot speak to -- but that sentence was removed.

Q. Well, would you agree with me that if Janssen removed that sentence, that the FDA would be expected -- actually, let me step back. Who removed that sentence, Janssen or FDA?

A. Janssen would have removed this and proposed in their revised label to the FDA, and the FDA would have agreed.

Q. And FDA then removed the language, correct?

A. That is -- would be my understanding.

Q. And so the FDA would have given careful consideration to that decision, correct?

A. Yes.

Q. And does that tell you that the FDA didn't consider that sentence to be important, given the totality of the label?

A. Yes, that is -- that's possible they did not consider that sentence to be important.

Q. Can you think of another explanation?

A. FDA reviewers, they are -- their effort is to make the labeling as user-friendly as possible as -- stating an opinion concisely and clearly. I don't know whether they considered that important, not important, but I think it was removed.
Q. They wouldn't remove something that they thought was important to be there, correct?
A. That is correct.
Q. Now, you testified on direct about the clinical trials portion of the various labels, correct?
A. That is correct.
Q. And the experimental evidence obtained during the clinical trials that are referenced in the labels showed an overall improvement in survival benefit for the combination of abiraterone acetate and prednisone, correct?
A. Yes. That is correct.
Q. And by contrast, the FDA has never found abiraterone acetate monotherapy, meaning the administration of abiraterone alone, to be safe and effective for treating metastatic castration-resistant prostate cancer, correct?
A. I believe that these trials of abiraterone monotherapy to prove these pivotal trials, they have not been done. So I don't know if you are saying the FDA did not find it or --
Q. Well, I'm asking a real direct question.
A. Right.
Q. It's true, isn't it, that FDA never found or concluded

that abiraterone acetate monotherapy is safe and effective for treating metastatic castration-resistant prostate cancer, correct?

A. Some sponsor, they have to submit the data to FDA for review. FDA cannot in a vacuum create that -- you know, make that judgment.

Q. So FDA did not find abiraterone monotherapy to be safe and effective in its own right, correct?

A. That's incorrect, because FDA would have to -- nobody submitted -- nobody submitted any kind of pivotal clinical trial studies on abiraterone acetate monotherapy to the FDA, so I think that would be incorrect statement.

Q. I'm not clear what you're saying.

Is it true that the FDA never found abiraterone acetate monotherapy to be safe and effective for treating metastatic castration-resistant prostate cancer?

A. That is an incorrect statement.

Q. Incorrect?

A. Yes.

Q. Let's pull out your July 19th deposition again. Let's turn to page 171.

A. What is the page number?

Q. 171, sir.

I am going to start on line 21. Tell me when you're there. Are you there, sir?

A. Right, uh-huh.
Q. And were you asked the following questions and did you give the following answers:
"QUESTION: The FDA has never found abiraterone acetate monotherapy to be safe and effective for treating metastatic castration-resistant prostate cancer, correct?
"ANSWER: It is not approved as a monotherapy.
"QUESTION: And the FDA has never found prednisone monotherapy to be safe and effective for the treatment of metastatic castration-resistant prostate cancer, correct?
"ANSWER: That is correct."
Did you give those answers to those questions, sir?
A. Yes, I did.
Q. And you were under oath, right?
A. Yes.
Q. And likewise, the FDA has never found prednisone monotherapy to be safe and effective for the treatment of metastatic castration-resistant prostate cancer, true?
A. Could you repeat your question. Why --
Q. It's true, isn't it, that the FDA never found prednisone monotherapy to be safe and effective for the treatment of metastatic castration-resistant prostate cancer?
A. That is correct. Uh-huh.
Q. And in deciding that abiraterone in combination with prednisone is effective for the treatment of metastatic

castration-resistant prostate cancer, the FDA had before it Cougar's phase I, phase II, and phase III clinical trial results, correct?

A. Yes, they would have reviewed it.

Q. They would have reviewed that, right?

A. Right.

Q. And did the FDA have phase II clinical studies before it showing the efficacy of abiraterone alone?

Let me rephrase it.

A. Yes.

Q. Did the FDA have phase II clinical studies before it supporting the efficacy of abiraterone alone?

A. Yes.

Q. Did the FDA also have phase II studies supporting the efficacy of the combination of abiraterone and prednisone?

A. The phase II studies are generally not adequately well-controlled to support efficacy. So they would have phase II studies for abiraterone acetate but those --

Q. I'm sorry. Let's back up.

You just agreed with me that they had phase II clinical studies before it with respect to abiraterone. I'm just asking you, did they have phase II clinical studies that were directed to the efficacy of the combination of abiraterone and prednisone?

A. They would have had phase II studies before their pivotal

studies.
Q. And they could compare for themselves the results from abiraterone monotherapy with the results from abiraterone together with prednisone if they wished to do so, correct?
A. Are you telling that -- that abiraterone monotherapy -- the phase II studies were -- yeah, they would have compared. Yes. Uh-huh.
Q. And did the FDA also have before it the de Bono extension study?
A. Yes, if it was submitted to FDA.
Q. And they're expected to review all the materials submitted to them, correct?
A. Yes, that is correct.
Q. That's what you did when you worked for FDA, correct?
A. Right.
Q. Now, you yourself do not have any experience reviewing clinical trials for prostate cancer, correct?
A. Not for prostate cancers but for other cancer.
Q. Not for prostate cancer, true?
A. That is true.
Q. And you don't recall having any experience in the design of clinical trials for prostate cancer, correct?
A. Not specifically to prostate cancer, that's correct.
Q. Now, I think you testified on direct that the FDA concluded based on the clinical studies presented to it that

abiraterone acetate in combination with prednisone is effective for the treatment of prostate cancer, specifically mCRPC, correct?

A. FDA -- the Zytiga® is effective for treatment of mCRPC.

Q. That wasn't my question.

A. Uh-huh.

Q. Did the FDA have clinical studies before it, such as phase III studies, that were sufficient to allow the FDA to conclude that abiraterone acetate in combination with prednisone is safe and effective for the treatment of prostate cancer?

A. Yes, that is correct.

Q. From the phase III Cougar studies, can you tease out the extent of contribution from prednisone individually or abiraterone acetate individually?

A. No, you cannot.

Q. And you're not saying that prednisone's contribution is necessarily zero based on those studies, are you?

A. The prednisone's -- this trial design doesn't answer that question.

Q. You can't tease that information out of the phase III studies, correct?

A. Phase III studies are not designed to attribute anti-cancer efficacy for prednisone because prednisone is there in both the arms.

Q. So you can't say based on those studies to what extent prednisone has anti-cancer benefit, correct?
A. The entire benefit could come from Zytiga®.
Q. I'm asking you, it could come from the combination of abiraterone and prednisone as well, correct?
A. It could come from abiraterone and prednisone. Like I said, trials are not designed that way. You have prednisone in both the arms --
Q. You've answered my question.
A. Uh-huh.
Q. It's possible that prednisone is reversing the resistance to abiraterone and contributing to the anti-cancer effect in the phase III study, correct?
A. There is not a shred of evidence to that in the records that I have reviewed.
Q. Did you review the phase II de Bono extension study?
A. I have reviewed the studies, the papers, the Attard paper. There is not -- there is no evidence.
Q. So you reviewed the Attard 2008 and 2009 studies or articles and you did not find a shred of evidence that prednisone was providing an additive anti-cancer benefit to abiraterone?
A. There could be some fact. The point is that this data or the trial designs are not adequate enough, not well-controlled enough for the FDA to consider them -- consider that prednisone

is providing anti-cancer effect.
Q. I'm not getting to whether they are sufficiently well-controlled studies for the FDA to rely on them. I'm picking up on your testimony that there's not a shred of evidence that prednisone provides an anti-cancer benefit in the combination with abiraterone. The de Bono study provides that evidence, doesn't it?
A. I'm talking from the FDA's perspective, FDA's lens, that to get the approval for -- as anti-cancer efficacy role for prednisone, that data is insufficient, inadequate for that.
Q. That's not my question. Would you agree with me that the de Bono study provides evidence that prednisone provides an anti-cancer benefit when combined with abiraterone, yes or no?
A. Theoretically, yes. I mean, this is a trusting hypothesis.
Q. Well, it is more than a hypothesis. He published data that supported that, correct?
A. Like I said, the data are published but this is still -- still stays a hypothesis that from the FDA point of view it would be insufficient to be considered granting a new indication for prednisone, a drug that has -- you know, that has never been approved by FDA as an anti-cancer drug.
Q. As I said, I'm going to get back to that, I promise you, and you can make your -- you can provide that testimony on redirect. I'm asking you a very specific question. The

de Bono extension study, as you read it, provides evidence that prednisone provides an anti-cancer benefit when combined with abiraterone, correct?

A. It provides some data to that effect. It provides some data.

Q. That's what I'm asking --

A. Yes.

Q. And that data was presented to the FDA, correct?

A. Yes.

Q. And by the way, the FDA does approve certain drugs based on phase II studies alone, correct?

A. They could.

Q. Okay. They have approved studies when -- strike that. I'll withdraw that.

Now, if the FDA believed that prednisone was only there for side effects, could the FDA have the label state in the indications and usage section that abiraterone acetate treats the disease and prednisone treats the side effects of abiraterone acetate?

A. Could the FDA allow?

Q. Could the label state that -- if the prednisone is truly only there for side effects, could the FDA have the label state in the indications and usage section that, abiraterone acetate treats the disease, the prostate cancer, and prednisone treats the side effects?

A. It will not be there in the indication and uses section, just there for -- if it is there for the side effects.
Q. Didn't we just look at a label where prednisone was identified as being for palliative purposes?
A. Yes, we looked at the label.
Q. So the FDA could have required the statement in the indications and usage section to say abiraterone acetate is to treat the cancer and prednisone is for side effects. They could have required that, right?
A. You're talking about two different drugs here. Zytiga® is an anti-cancer drug. You're talking about prednisone monotherapy that is well-known for many decades what their role is and how these drugs work.
Q. Let's try a simple answer to my question. Could they approve -- if they really -- strike that.

If they really believed that abiraterone is the only drug in the combination that treats the prostate cancer and that prednisone is solely, solely for treating side effects, could they permit a label, could they authorize a label that says in the indications and usage section that abiraterone treats the prostate cancer and prednisone is for the side effects of abiraterone acetate, yes or no?
A. The indication and uses section lists the drugs that is -- that are for safe and effective use. So they could have -- they could have allowed it.

Q. And they also could approve an indication and usage section that has abiraterone, under your view, in the indications and usage section for treating the prostate cancer and they could remove the prednisone entirely from the indications section and put it only in the side effects or warnings section, correct?
A. That is a possibility, yes.
Q. And if they wanted to call people's special attention to serious side effects that could be caused from abiraterone acetate and that you need to take prednisone to counteract those, they could have a black box warning, correct?
A. The black box warnings are given for entirely different -- different purposes.
Q. You've seen black box warnings?
A. Yes, I have.
Q. Have you seen black box warnings indicating for one anti-cancer drug that it needs to be co-administered with a glucocorticoid?
A. I have not seen it.
Q. Did you hear Dr. Rettig's testimony about that yesterday?
A. I heard about it, but --
Q. You were here, right?
A. I was here.
THE COURT: Mr. Rein, at a convenient point.
MR. REIN: Pardon?

THE COURT: Any convenient point --

MR. REIN: I can break now.

THE COURT: Now would be good?

From the point of view of this case, we're taking a break, and we will reconvene at 1:45. Let's clear the well because I have another matter.

(Recess taken 12:00 p.m. through 1:45 p.m.)

THE COURT: Good afternoon. Be seated. Whenever you're ready.

MR. REIN: Thank you, Your Honor.

BY MR. REIN:

Q. Dr. Nagaich, I assume you did not talk to counsel about this case or your testimony during the break; is that true?

A. I haven't talked to.

Q. Now, picking up from where we left off before the lunch break, the FDA concluded, based on studies presented to it, that the combination of abiraterone acetate and prednisone are safe and effective for the treatment of advanced prostate cancer, correct?

A. That is correct.

Q. And the FDA was made aware that the combination had a survival benefit, meaning it saved lives, correct?

A. Yes. That is correct.

Q. And so it's important when there's an anti-cancer treatment that saves lives for it to be made available to

patients as soon as possible, correct?
A. That is correct.
Q. Now, as you also testified before the break, you can't tease out whether or to what extent the prednisone contributes to the efficacy based on the phase III studies, true?
A. Yes.
Q. Now, if the FDA required the label to say that abiraterone is to treat the cancer and prednisone should be used as needed for side effects or if prednisone is only in the warnings section with respect to side effects, wouldn't that make it more likely that clinicians would administer abiraterone acetate without prednisone?
A. No.
Q. So if prednisone is just in the warnings section as something that should be administered to counteract abiraterone side effects and the indication and use only said abiraterone to treat the prostate cancer, you're saying that clinicians would uniformly utilize the combination in any event?
A. No. I think if prednisone is there only for the side effects -- could you -- I'm sorry. Could you restate your question.
Q. Sure.
A. I want to ensure that I answer your question correctly.
Q. If the label were such that the indications and use section simply said abiraterone is to be administered in

1000 milligrams --
A. Right.
Q. -- to treat the prostate cancer and then the prednisone is only in the warnings portion of the label and indicates that prednisone is to counteract side effects from abiraterone, do you think clinicians would administer the combination as commonly as they do under the current label?
A. No, they will not.
Q. And if prednisone contributes to abiraterone's efficacy, then if clinicians simply administered abiraterone alone, that could end up costing patients their lives; isn't that right?
A. Yes, if it -- if this is not safe administering abiraterone acetate alone.
Q. No, that's not my question.

If abiraterone needs prednisone to compound the anti-cancer effect, which is possible based on the phase III studies, and clinicians only see prednisone in the side effects section and administer abiraterone as a monotherapy, the result could be that prostate cancer patients would not survive as long, true?
A. That is not correct. Let me -- let me just explain it to you.

Typically --
Q. I don't need an explanation. I want to know if clinicians administered only abiraterone and the combination is

responsible for added efficacy, the net result would be a loss of survival benefit, yes?
A. That is true, right.
Q. So the best practice to ensure maximum efficacy in view of all the clinical data is to specify what is specified precisely in the Zytiga® indications and usage portion of the label, correct?
A. Not for the efficacy. Safety and efficacy.
Q. I'm sorry. The best way to make clinicians co-administer abiraterone and prednisone together is to put in the indications and usage section that both should be administered together, correct?
A. Yes. If there is a major safety concern --
Q. Whether it's safety or efficacy, the best way to get the clinicians to give them together is to -- is to put in the indications and usage section that they should be co-administered, correct?
A. Yes.
Q. And in terms of whether the FDA believed that there was a significant chance that prednisone contributed or contributes to the efficacy, they had before them the phase II clinical studies, such as the de Bono study, that they could have looked at, correct?
A. The de Bono study is not adequate and well-controlled study for FDA to make a determination whether prednisone has

any efficacy as an anti-cancer drug.
Q. We've already established that the FDA has very good policy reasons for wanting the two drugs to be co-administered to patients, correct?
A. It depends.
Q. Assuming that there's a chance that prednisone contributes to the efficacy, then the FDA wants those two to be co-administered, isn't that true, Dr. Nagaich?
A. They could potentially consider that -- this is not a combination therapy. I think they could consider this as combination therapy if prednisone had any effect as an anti-cancer.
Q. I'm not sure you're answering my question, sir.
Isn't it true that -- given that the FDA has concluded that the combination is safe and effective --
A. Right.
Q. -- it wants the clinicians to administer the combination, right?
A. It wants the physicians to co-administer --
Q. Right.
A. -- the drug, Zytiga® with prednisone.
Q. That's right.
A. Uh-huh.
Q. And it has phase III studies that prove that the co-administration will result in saving lives, correct?

A. Phase III study suggested that Zytiga® and prednisone is both safe and effective and it saves lives. That is true.
Q. And it also has perhaps not a well-controlled study like you would like, but it has clinical data through the de Bono extension study, among other things, for it to want to make sure that prednisone is included with abiraterone because of its potential efficacy benefits, correct?
A. That is not correct.
Q. So you think that they want -- they should want to take a chance that prednisone is important to the efficacy and risk lives?
A. I'm not understanding your question. I think --
Q. They --
A. -- prednisone is here for safety.
Q. You're saying that, but you will agree with me that you can't tease out to what extent prednisone contributes to efficacy from the phase IIIs, correct?
A. That is correct.
Q. So you don't want to take a chance, do you? You want them to be co-administered, right?
A. You want them to be co-administered; that is true, yes.
Q. And you don't want to lead to delay, do you?
A. That is the FDA's -- this was given a priority review, and this is an important therapy.
Q. All right.

A. Definitely, yes.
Q. Just so we're clear following up on the Court's question of you, what kind of well-controlled study would be able to tease out to what extent prednisone contributes to the anti-cancer benefit?
A. As I said before, I think there has to be an abiraterone monotherapy trial or some other adaptive clinical trial design. I just cannot think off the top of my head. But definitely Janssen will have to provide that data to FDA to prove that prednisone has an anti-cancer role here.
Q. I need more specifics here. How many arms do we need for this well-controlled study to tease out the benefits of prednisone?
A. At a minimum, three arms.
Q. What would the three arms be?
A. It would be you have to -- in the 301 study design, you will have to include an abiraterone acetate monotherapy arm.
Q. And what else?
A. You would have, then, placebo prednisone. You will have abiraterone acetate placebo. And then you will have the current abiraterone acetate/prednisone.
Q. All right. So when you say "three arms," patients don't have three arms. You're talking about three groups of patients, correct?
A. Absolutely.

Q. How big would the groups of patients have to be?

THE COURT: Now, that would be a side effect.

MR. REIN: Right.

THE WITNESS: I can't answer this, but -- how big, because it requires a lot of input. I'm not an expert in clinical trial design. I have reviewed these pivotal studies, so I would defer this to somebody who -- it certainly has to be a large -- large group, almost similar to what they have done before.

Q. Well, in the Zytiga® phase III studies, they had, what, over a thousand patients?

A. Yes.

Q. And if you have three arms, you need a lot more than that, don't you?

A. Potentially, yes.

Q. And how long -- would you need tens of thousands of people?

A. No. I don't -- I don't think so.

Q. And I'm just trying to make sure I understand how many arms there are. Let's count them up.

Abiraterone acetate monotherapy. That's one, right?

A. Right.

Q. And placebo plus prednisone, is that another?

A. Placebo plus prednisone.

Q. Okay. Placebo plus abiraterone acetate, is that another?

A. Placebo.
Q. Plus abiraterone acetate, wouldn't that be required?
A. Placebo plus abiraterone acetate would be required.
Q. And what about abiraterone plus prednisone? That would be required?
A. I just want to make sure that I answer you correctly.
What is the first arm? I'm sorry.
Q. Abiraterone acetate monotherapy.
A. Okay. Uh-huh.
Q. Then you'd need placebo plus prednisone?
A. Placebo plus prednisone.
Q. Yes?
A. Yes.
Q. Then you'd need placebo plus abiraterone acetate?
A. So you need a -- so the current design is, you have prednisone plus abiraterone acetate in one arm and what Janssen has is placebo plus prednisone. But you need a third arm, is placebo plus abiraterone acetate.
Q. And so you wouldn't have abiraterone alone in another arm?
A. That's what I said. It has to be placebo.
Q. Plus abiraterone?
A. Right.
Q. So there would no arm that's abiraterone alone?
THE COURT: With no placebo you mean?
THE WITNESS: With no placebo.

BY MR. REIN:
Q. With no placebo.
A. Right.
Q. Okay. So three arms.
So back to the number of people you'd need, there were 1,000 people with the two-arm study. How many would you need for a three-arm study?
When I say "1,000," there were actually more, right?
A. Like I said, I'm not an expert in clinical trial design but at least you will need these three arms for --
Q. So --
A. -- to control for the studies.
Q. Can you guesstimate for us how many more than 1,000 people you would need?
A. Cancer trials are not like vaccine trials where you need 3,000 or 10,000 patients. I think it should be in the same range that Janssen had used in the other -- for the other arms.
Q. Well, we had two groups of over 1,000 people, so you would need at least another 500 people?
A. Potentially, yes.
Q. Okay. And so -- yeah, by the way, do you need placebo plus placebo?
A. Ideally you would need; but if this is not ethically possible, then this is against the trial, then you won't need this.

Q. Oh, ethics, let's talk about ethics. First of all, how long would this trial take?
A. I -- I can't answer this question off the top of my head how long this trial will take.
Q. A year, two years?
A. It depends. You know, when you start recruiting patients, a trial -- how long is the design phase of the trial. It could take -- drag on, so I just cannot put a timeframe on that.
Q. It could take many years, right?
A. I cannot answer that.
Q. All right. And so meanwhile, since we have at least three groups, two of them don't have abiraterone plus prednisone, right? Two of the groups do not have abiraterone acetate and prednisone, correct?
A. Two of the groups, they don't have abiraterone acetate plus prednisone --
Q. Correct. There's only one arm that has abiraterone plus prednisone, correct?
I think it's pretty simple.
A. Right.
Q. You'd have three groups, one of them had prednisone and abiraterone. That leaves two groups without that combination, true?
THE COURT: One or the other is a placebo is what you're saying?

THE WITNESS: Right.

MR. REIN: Well, you've got -- well, he's got one that has placebo plus abiraterone. He's got one that has placebo plus prednisone.

BY MR. REIN:

Q. Those two do not have the combination of abiraterone and prednisone that could be the magic formula, right?

A. Right. You have to have an arm with a placebo, abiraterone acetate, and prednisone.

So you have -- you need the -- if you want to tease out just the effect of abiraterone --

Q. No, prednisone.

A. -- from prednisone, you just need maybe two. You need the current therapy where you could have the combination, abiraterone, prednisone, and then you can have just the abiraterone with placebo.

Q. So just two arms you could do?

A. Yeah, two.

Q. You don't need a placebo?

A. Yeah, you don't need that.

Q. And if abiraterone and prednisone are important for extending lives and survival benefit, there would be a ethical problem giving people things that they didn't know had that survival benefit, true?

A. Potentially.

Q. And the IRB wouldn't approve a study that had ethical concerns, true?
A. That is -- that is correct.
Q. So what we're left back with is the question for you, how do you design, develop, and implement a study beyond what was done here to tease out the prednisone effects without causing ethical concerns?
A. Well, that is -- that is the point that there is -- you cannot design a trial where you want to claim that prednisone has an anti-cancer effect.
Q. Basically you either -- so what you're saying is that the FDA under these circumstances couldn't look at -- well, let me take a step back.

You mentioned before that sometimes the FDA looks at just phase II studies, correct?
A. FDA has the authority to look at the phase II studies only and grant an approval, but these are extreme circumstances and depends.
Q. Well, it's an extreme circumstance when you know that the combination is efficacious to save lives but you don't know for sure to what extent prednisone contributes, wouldn't that warrant looking at the phase II studies to see if there's enough evidence there to justify putting in the indications and use section that both of them are for the treatment of prostate cancer?

A. Not necessarily.
Q. But it is a -- it's -- you say "not necessarily." It's something the FDA could do, correct?
A. FDA could also do the alternative. If FDA finds that prednisone -- that Zytiga®'s side effects are inherent to its basic mechanism of action, that leads to the lowering of cortisol --
Q. You're not answering my question.
A. No, I'm answering your question.
Q. No. My question, sir, is whether FDA in the circumstances that I just described, when it knows that the combination therapy is saving lives and it has information that suggests -- from phase II clinical studies that suggest that prednisone and abiraterone both contribute to that, it would be a sound and reasonable thing for the FDA to do to approve an indication that called for physicians to co-administer them together, correct?
A. Based on the data that I have reviewed, there is no evidence to suggest that prednisone has any kind of efficacy as an anti-cancer.
You're asking me to answer a hypothetical question, sir.
Q. Well, let's start with my hypothetical --
A. Right.
Q. -- and then we'll kind of --

A. Sure.
Q. -- go from there.
In my hypothetical, assuming that the FDA has phase II studies that are suggestive that both abiraterone and prednisone contribute to the anti-cancer effect, then it would be fair and reasonable for FDA to indicate that both of them have an anti-cancer effect under these circumstances when it wants doctors to co-administer them, correct?
A. That is up to FDA to determine how they want to view the efficacy data that Janssen would present to them.
Q. Okay. And so what you're saying is, you don't think that the de Bono extension study is sufficiently compelling for your purposes; is that right?
A. It is not sufficiently compelling for FDA to consider -- from the FDA point of view to consider that this has role in efficacy.
Q. But, see, here is the issue, Doctor. FDA is going to approve a combination of the two which it knows collectively provides the benefit, and it wants the patients to get the combination. It doesn't have to have a well-controlled study to tease out prednisone's effects under these circumstances, true?
A. FDA -- that is true. The point is that FDA is considering that prednisone is required for the safety of Zytiga® and --
Q. If FDA concludes that it's possible that it's contributing

to the efficacy and it needs it for the safety, it would want the two to be taken together, correct?

A. For efficacy claim you would require -- you would require a trial -- a separate trial. I mean, I'm not understanding your question, sir. Could you repeat it.

Q. I think you well understand my point and my question.

My question is, under these circumstances, these extreme circumstances when FDA already has evidence, compelling evidence that the combination is safe and effective and that it's saving lives and it wants doctors to co-administer them, and it also has evidence that each of them may be contributing to the efficacy, then it is perfectly fair and reasonable for them to accept the clinical evidence that they have and approve the label as is, true?

A. Not true. I think what you're saying here that FDA -- FDA is assuming -- you are -- that -- you are thinking that FDA thinks that there is efficacy associated with prednisone. I think what F -- looking at all the evidence, prednisone is for safety --

Q. Sir, FDA is just as smart or smarter than you are, aren't they? Collectively?

A. What is that?

Q. That's a bad question. Let me try it this way.

There's a lot of experts at FDA, correct?

A. That is correct.

Q. And they would understand, just like you, that from the phase III clinical study you can't tease out to what extent prednisone contributes to the efficacy, true?
A. From the current phase III studies, you cannot tease out --
Q. They would understand that --
A. -- efficacy --
Q. They would understand that, right, sir?
A. They would understand that.
Q. And so they would also understand, as a consequence, the importance of clinicians prescribing the combination because they can't tease out the differences, right?
A. That's correct.
Q. And so -- and they don't want to get bogged down and delayed and have a three-arm study that ends up costing lives, true?
A. That is up to the FDA.
Q. Right. And so they also have before them phase II data that suggests that prednisone has the ability to reverse resistance to abiraterone. They have that data, correct?
A. Yes, they have that data. Yes. Uh-huh.
Q. And so they would be warranted to indicate in the indications and use that the combination should be used to treat the cancer, correct?
A. The combination -- like I said, the combination

alternative possibility is -- the data suggests is that -- that the basic mechanism by which Zytiga® works requires co-administration of prednisone for the safe use of Zytiga®. That is what the data suggests, sir.

Q. Do you want them to put Zytiga® solely in the warning -- I'm sorry.

Do you want them to put prednisone only in the warning section and risk that patients don't -- that clinicians don't co-administer? Is that what you think should be done?

A. No, I don't think that should be done. I think the FDA has decided to put this in the indication and usage section --

Q. And they --

A. -- because --

Q. Right. That's what they decided. And they did not require Janssen to state that prednisone is only there for side effects, true?

A. But the data suggests that prednisone is there for the side effects.

Q. You keep saying that, sir, but the data -- you can't tweeze out from the data to what extent prednisone is contributing to efficacy, right?

A. I'm talking about the side effects, sir.

Q. I'm talking about efficacy.

You can't tweeze out to what extent prednisone is contributing to the efficacy, true?

A. Prednisone is there in both arms, and this is study -- the phase III is controlled for Zytiga® --
Q. Are you --
A. -- it's not controlled --
Q. Are you backing away from your testimony that you can't tweeze out to what extent prednisone contributes to efficacy?
A. No, I'm not backing out of it.
Q. Okay. I'll move on.

Let's talk about the timeline that you put on the screen, DDX 2100.15. You testified that after the pre-IND meeting FDA reviews the IND; and then if they're satisfied there are no safety concerns with the proposed protocol and the drug, they allow the study to proceed, right?
A. That is correct.
Q. And you next testified about correspondence between Cougar and FDA regarding whether glucocorticoids should be added as needed or should be co-administered. Do you remember talking about that?
A. Yes, that's right.
Q. And you pointed out that in the end the FDA required co-administration, correct?
A. That is correct.
Q. But you left out an important fact, Dr. Nagaich. You left out that the IND allowed Janssen to proceed with an abiraterone monotherapy, right?

A. Right. Yes. Uh-huh.
Q. That means that the FDA concluded that abiraterone when administered alone, as a monotherapy, was safe, right?
A. Safe for -- what study are you talking about? I'm just confused.
Q. The IND --
A. Uh-huh.
Q. -- approved -- approved is probably the wrong word but gave Janssen the go-ahead to proceed with the monotherapy study of abiraterone that it proceeded to do, correct?
A. They would have looked at the critical protocol that Janssen would have submitted with their IND, and they would have determined that the protocol looks okay for them to proceed. Up until that point they would not have discovered any safety issue. IND is -- this is the first in-human trial, and after the phase I data are being gathered, safety issues will pop up at that time.
Q. I understand that, sir, but the protocol that the IND authorized to go forward or that it allowed to go forward was a monotherapy, right?
A. Up till that point FDA will not know what the safety concerns are because it's just -- the clinical studies have not been done.
Q. But didn't you tell us that before an IND there's a meeting and the FDA reviews all sorts of animal data and the

like and makes a safety determination, true?
A. Safety determination, there are concerns for safety. And then based on the questions that Janssen wanted to discuss with the FDA, it was Janssen who are proposing prednisone's administration as needed.
Q. I think you mis- -- right. You misspoke, though.
The protocol that the IN -- that was before the board in connection with the IND was an abiraterone monotherapy study, correct?
A. Well, which -- I'm sorry. Which study you are talking about?
Q. You tell me. You've got this timeline here. It says pre-IND package.
A. Right.
Q. FDA meetings, meeting minutes, Cougar meeting minutes, so there are all these meetings and animal studies. And then you said an IND ends up issuing, and then the next step is that the applicant can go forward with his or her studies, correct?
A. Right.
Q. And my point is that the study that was under consideration was a monotherapy study of abiraterone alone, right?
A. That is fine, yes.
Q. And Janssen did proceed to perform studies with abiraterone acetate alone, correct?

A. Could you -- could you show me --
Q. Well, you have been sitting in court during this trial, right?
A. Right. Uh-huh.
Q. And you saw Mr. Charnas' testimony; you saw Dr. de Bono's testimony.
You are aware that the first studies done were monotherapy studies of abiraterone, right?
A. I believe there are other arms. I just cannot recall at this point sitting here. So I would appreciate if you can show it to me, the pre-IND briefing package.
Q. So you don't know one way or the other?
A. I can't recall at this point.
Q. Okay.
A. I would need to --
Q. But you do recall that the de Bono study began in December 2005.
Do you know that?
A. I don't know when it began, the study.
Q. Do you know when the results started coming in?
A. I don't recall right now the timeframe.
Q. You don't recall that they were in 2006 and early 2007?
A. I don't recall the timeframe.
Q. And when the results came in, Dr. de Bono and Cougar became aware that there was a potential efficacy benefit in the

combination of prednisone and abiraterone, correct?
A. They may have concluded from the studies. But, like I said, FDA --
Q. I'm not asking about FDA.
I'm asking whether they concluded that there was an efficacy benefit in the combination.
A. That must have been their hypothesis, right.
Q. And not only that, they published that hypothesis in many notable scientific journals, correct?
A. Yes, they did.
Q. And those were peer-reviewed, correct?
A. I believe so.
Q. And that means that scientists with, you know, a broad background and collagists and statisticians looked at the information, correct?
A. That is correct, yes.
Q. And many publications went on to publish the de Bono extension study and report about the exciting results, correct?
A. That may be -- that may be correct --
Q. Right.
A. -- but from the FDA point of view, these studies are not adequate --
Q. Well, actually --
A. -- to support --
Q. Go ahead.

A. -- efficacy claims for prednisone.
Q. I got the impression this morning -- didn't you tell us that none of those publications were submitted to the FDA?
A. Scientific publications, they are not part of FDA regulatory submissions that FDA reviews.
Q. So you're saying that none of the publications that describe the de Bono extension study were submitted to FDA?
A. They may have been submitted to the FDA but FDA does not rely on those papers.
Q. Well, I wrote a note where you said this morning that they weren't even submitted. Do you take that back?
A. I have not seen the entire submission package --
Q. So you don't know whether --
A. I don't know.
Q. You don't know.

And you would expect FDA to rely on materials that were submitted to them, right?
A. As an FDA reviewer, I know that scientific publications are not considered in FDA's decision-making process at any stage.
Q. Have you ever worked in the oncology area for FDA?
A. I have worked on oncology area.
Q. Did you work in the FDA oncology unit?
A. Not in the oncology unit, but I have reviewed drugs indicated for cancer.

Q. Have you spoken to people in the oncology unit to see what their practices were?
A. I have not spoken to the people in oncology.
Q. All right. Let's pull up Janssen Research & Development document --
MR. REIN: Matt, it's...
(Discussion held off the record.)
MR. REIN: If we can blow that up.
BY MR. REIN:
Q. This is a document entitled Clinical Summary. This is something that was --
MR. REIN: Why don't we turn to the next page.
MR. WONG: I don't think this was before the Court in the exhibit list. And it's not in the witness' binder. I don't think the witness has it either. Or the Court.
MR. REIN: I'm happy to --
THE COURT: Yes. What was that exhibit number again?
MR. REIN: So this is, I think -- it does not have an exhibit number on it, Your Honor. I'm using it for cross. I am happy to hand it out, though.
THE COURT: Yes. Let's see it.
MR. REIN: May I approach the witness, Your Honor?
THE COURT: Yes, and me.
MR. REIN: And the Court?
THE COURT: Thanks.

Let's call this something. We can call it Exhibit 1 million if you want to, but we just need to be able to see what it was when we look at the record some day.

MR. REIN: Understood.

BY MR. REIN:

Q. Let's look at the second page.

This is identified at the top as a module 2.7.5 entitled Clinical Summary Literary References.

Do you see that?

A. I see that.

Q. And do you recognize this document, sir? Have you seen it before?

A. I have not seen this document before.

Q. Do you know if this document was submitted in connection with one of Janssen's NDA submissions?

A. Like I said, I have not seen this document before, but it looks like it's module 2.7.5. It may have been submitted with NDA. But like I said, I have not seen this document.

Q. What is the significance of module 5.4 to you -- or module number?

A. It's the clinical summary data are provided in that module.

Q. To -- in an FDA NDA submission, correct?

A. Yes.

Q. All right. And do you notice there's a list of -- a

summary of -- well, let's look.

References. The references listed below are located in module 5.4 unless marked by an asterisk.

Do you see that?

A. Yes, I see that.

Q. And among the listed references are Attard 2008 and Attard 2009.

Do you recognize those references?

A. Yes.

Q. Those describe the exciting results from the de Bono extension study, correct?

A. Yeah. Those two papers talk about the results, yes.

Q. And those were peer-reviewed, right?

A. I believe this is a peer-reviewed journal, so --

Q. And do you also see reference number 6 below, Danila? Danila?

A. Yes, I see that.

Q. And do you recall that being discussed during Dr. Rettig's testimony?

A. I don't specifically recall, but it may have been discussed. I don't recall.

Q. So this shows that the oncology unit does from time to time receive publications in connection with NDA submissions, right?

A. These references are cited or could be cited. But like I

said, FDA does not consider data provided in these scientific publications as a basis for their review and approval work.

Q. Well, again, we're talking about an unusual special circumstance where the FDA wants to get the combination in the hands of patients and clinicians, right?

A. No matter what the circumstances are, sir, FDA will not consider scientific publications as a basis for their review and approval work.

Q. Do they -- do they consider phase II clinical results?

A. That is up to the FDA for extreme circumstances. The secretary -- as the regulations say, the secretary is allowed to approve a drug just with the phase II studies. But that is up to the FDA, and that happens when you have a critical, unmet medical need.

Q. And the Janssen or Cougar phase II study, there is one that reflected the de Bono -- that contains the de Bono study, correct?

A. This a study that is -- certainly offers advantage than the existing therapies. But I believe it may not -- it's up to FDA. I believe this would not meet the criteria of -- of --

Q. Well, the FDA doesn't need to rely on that alone because prednisone is being co-administered with abiraterone, right? And it has phase III studies that relate to the co-administration of the two, true? Correct?

A. Phase III studies are, like I said, they are not

supported -- they are not supportive of any kind of clinical efficacy for prednisone.

Q. That's not my point.

FDA is relying on the phase III studies to justify giving the two in combination to patients, right?

A. There is enough evidence in the NDA submission that the role of prednisone is to address safety.

Q. That isn't my question. You keep wanting to go back to that mantra.

But my question is whether the two -- whether the clinical studies, phase III studies, support the safety and efficacy of the combination for advanced prostate cancer.

We've already established that, right?

A. Well, you see, it's a combination product. Different use. I have a different image in my mind. This is not a combination product.

This is a co-administration of two drugs which have an independent, different pharmaceutical class. They have different package inserts. They have been indicated for different indications --

Q. Let's use your word, "co-administration."

The FDA has sufficient phase III clinical study data to support the safety and efficacy and survival benefit for the co-administration of those two drugs for advanced prostate cancer, true?

A. Yes.
Q. And the only thing they need to look at phase II studies for is to see if there is clinical support that the prednisone has an anti-cancer benefit because, really, it doesn't matter whether it does or it doesn't, so long as the clinicians prescribe them together, true?
A. Sir, regulations require that indications, newer indications, they must be supported with adequate and well-controlled clinical studies.

So even if you have some phase II data that is preliminary data that talks about efficacy of prednisone, it's not sufficient data for the FDA to approve a new indication for a drug that -- drug class that has never been considered for -- or never been approved by the FDA for any kind of anti-cancer use.
Q. All right. So your preference would be to take prednisone out of the indications and use, put in the warnings section, and risk losing lives because physicians administer abiraterone alone? Is that what FDA would prefer to see happen?
A. I would say the FDA is concerned about safety, first, and then the efficacy of the drug. So I think it could work both way. If FDA determines it's not safe --
Q. But here's the problem I have with your analysis: The FDA has concluded that the combination is safe, right?
A. Yes, the combination. When Zytiga® is given in

combination with prednisone, it is safe and effective.
Q. Right. They've concluded that it's both safe and effective, right?
So they have everything that they need in order to -- to instruct physicians to administer the two in combination, correct?
A. That is -- that's why the drug is approved.
Q. Right. And what they don't want to see is a bottleneck and a delay in getting the drugs to the doctors and the patients, right?
A. I'm -- I'm not understanding your question.
Q. Would you like them to force Janssen to do a three-arm study before they -- before accepting a claim that prednisone has an anti-cancer effect?
A. No. I think this is -- they accepted the study. They approved the study, and the product is approved.
The point that Janssen is trying to make, that the prednisone has anti-cancer role in this combination. The data that FDA has reviewed and that I have reviewed doesn't suggest that. So if the drug is approved, it's a good drug. It's approved for patients who have metastatic castration-resistant prostate cancer. But prednisone's role in this drug, this -- for safe use of Zytiga®, there is plenty of evidence for that.
Q. You keep repeating that. But you told me, didn't you, that prednisone may be contributing to efficacy, right?

A. No, sir. I did not say that. I said there is no -- that trial, clinical trial design, they cannot parse out the role of prednisone. That's what my statement is.
Q. That means that prednisone may be contributing to the efficacy, right?
A. Maybe Zytiga® is contributing to hundred percent efficacy.
Q. Maybe, and maybe the combination is necessary for the efficacy, right?
A. The data, sir, suggests that the combination is necessary for the safe and effective use of this drug.
Q. And the data suggests that prednisone is an integral part of that combination, correct?
A. The prednisone is an integral part to provide safe use of Zytiga®.
Q. And it may be an integral part of the efficacy as well. You just don't know, right?
A. The current trial design don't attribute any kind of efficacy role to prednisone.
Q. But the trial design doesn't allow you to tell one way or the other whether the prednisone is contributing to efficacy, true?
A. The trial designs are controlled for Zytiga®, so Zytiga® is efficacious.
Q. The combination --
A. Prednisone is in both arms.

Q. The combination is efficacious, right?

MR. WONG: Your Honor, I think we have the witness' answer on this.

MR. REIN: Yeah. I'll move on.

BY MR. REIN:

Q. And let's go to the second entry on your timeline.

THE COURT: Excuse me.

Go ahead.

BY MR. REIN:

Q. That entry says October 6, 2008, Cougar requires glucocorticoid administration and protocols.

Do you see that?

A. Yes.

Q. Were you suggesting that that was the first time that Cougar put in place protocols that co-administered a glucocorticoid with abiraterone?

A. After that modification -- after the fatality of the patient, they modified their clinical protocol that required administration of glucocorticoid with every patient.

Q. But there were other protocols that preceded the adverse incident with the patient that called for the co-administration of abiraterone and prednisone, correct?

A. That was on a need to -- need-to-use basis. They were not --

Q. I'm sorry. Were there earlier protocols that called for

the co-administration of prednisone and abiraterone, yes or no?
A. There may have been some studies. I cannot recall right now.
Q. Were you trying to suggest that this was the first time that a protocol was approved that involved the co-administration of prednisone with abiraterone?
A. No.
Q. So why did you highlight that one?
A. Because after -- after they had a serious adverse event, they modified the protocol and they required that Zytiga® must be administered along with prednisone.
Q. You were here when Dr. Charnas testified, weren't you?
A. Yes, I was.
Q. And let's look at amendment 5 to the 002 study, PTX 074.
MR. REIN: If we could highlight on the screen the date of amendment 5.
BY MR. REIN:
Q. May 25, 2007. Do you see that?
A. I see. I have not reviewed this document before.
MR. WONG: Can we get a copy, please? I don't think the witness has that.
MR. REIN: Happy to get you that.
BY MR. REIN:
Q. And so why don't you turn to page 3 of this document, 1.22, phase II. The first bullet point says: To assess the

safety and tolerability with concurrent prednisone.

Do you see that?

A. I haven't reviewed this document before, and I'll need time to review and analyze this before I -- you know, I can discuss this with you.

THE COURT: Pass me one of those --

MR. REIN: I will hand one to the witness, if I may.

THE COURT: And one to me.

MR. REIN: Sure.

BY MR. REIN:

Q. Have you seen this document before, sir?

A. This the COU-AA-002 study. Yes.

Q. Do you see the reference to amendment 5 on the front page?

A. Could you point me to where --

Q. Sure. The page -- the first page right towards the middle under Gloria Lee, do you see amendment 5 on the right, dated May 25, 2007?

A. Yes.

Q. That's the latest amendment that's listed?

A. Right.

Q. All right. Would this be amendment 5 of the protocol?

A. I believe so. I haven't -- like I said, I have not --

Q. Did you study all the clinical history of Zytiga®?

A. I studied whatever was provided --

Q. By whom? Provided --

A. By Janssen.
Q. I'm sorry?
A. By Janssen, whatever was provided.
Q. So you've reviewed all of Janssen's clinical documents in connection with your work on this case?
A. Not all of them, but --
Q. Did you just review the ones that were provided by defendants' counsel?
A. Yes. And those -- whatever I reviewed are cited in my expert reports.
Q. So you just reviewed the ones that defendants' counsel fed you, right?
A. Yes.
Q. And did you ask for all of the FDA documents?
A. Yes, I asked for all of them.
Q. And were you given them all?
A. Yes.
Q. So you would have seen this document?
A. I don't recall particularly this -- this document or this figure.
Q. Let's take a look at page 3.

Phase III (sic) is indicated as assessing the safety and tolerability of abiraterone with concurrent prednisone in the population, right?

A. What are you referring to here?

Q. Under 1.22.
A. Under 1.22, phase II study, yes.
Q. So this was a co-administration of prednisone and abiraterone that was put in place through a protocol dated May 25, 2007, correct?
A. Look, I haven't reviewed this document in a -- I need more time to analyze and discuss this with you.
Q. Sure. And --
THE COURT: Before you go on, though, help me out. What does CB7630 signify?
MR. REIN: Abiraterone acetate, Your Honor.
THE COURT: Okay.
BY MR. REIN:
Q. Well, I guess I should ask the witness: Are you aware that CB7630 is abiraterone?
A. Yes, I am aware of that.
Q. And the second bullet point indicates that one of the markers being assessed is PSA-based progression-free survival.
Do you see that?
A. Yes, I see that.
Q. Is that common in studies of advanced prostate cancer that are considered potentially to be hormone-driven?
A. It's a common test method for prostate cancer. It's not a validated biomarker by the FDA, though.
Q. Right, but it's -- when you say that, FDA looks at that in

combination with other factors as indicative of the activity, correct?
A. Yes. It is one of the tests.
Q. Now, May 25, 2007, the phase II portion of the 02 study, that already included abiraterone acetate plus prednisone prior to the patient death, correct?
A. I think I need more time to really answer your questions. I haven't reviewed this document.
Q. Well, let's try this.
MR. REIN: Why don't we put PDX 2.2 on the screen.
BY MR. REIN:
Q. Do you remember seeing this summary of clinical trials during Dr. Charnas' testimony?
A. Yes. I saw this slide. Yes.
Q. And according to -- did you check to see if this was consistent with your understanding of the clinical trials performed by Cougar and Janssen?
A. I haven't had time to really digest whatever is provided in this slide and then compare it with my notes, so...
Q. Defendants' counsel didn't provide this slide to you which was provided to them in litigation?
A. I haven't seen this slide. It was not provided to me.
Q. And does this indicate when the various protocols were approved?
A. Approved original protocol, I think it lists out the dates

for the protocol approval for each of these studies.
Q. And right. So let's start with the 002 study. That indicates that the protocol was approved on October 18, 2005, correct?
A. That's what it states.
THE COURT: Are you asking what your slide says?
MR. REIN: Well, I want to know if it's consistent -- I'll follow up and ask him whether it's consistent with --
THE COURT: Yes. If these dates mean something to him, fine. But --
MR. REIN: Sure.
BY MR. REIN:
Q. So this indicates that there were -- that the following protocols were in place that called for abiraterone together with prednisone before the one that's on your timeline, 002, 003, 004, and 301, if I'm not mistaken.
Do you know whether there were a number of protocols that were in place that called for the co-administration of glucocorticoid with -- or prednisone with abiraterone before the date that you indicated the change was made?
A. I'm aware of that -- that there were protocols that called for co-administration, but they were not -- but the prednisone administration was not there with every -- every dose or every patient.
Q. I don't understand that question (sic).

Were you aware that there were study protocols in place that called for the co-administration of prednisone and abiraterone --

A. Yes.

Q. -- prior to the patient death?

A. Yes. Uh-huh.

Q. All right. Let me just move to one -- I think one last topic.

You were shown a number of documents on Cougar's interactions with the FDA.

Do you recall that?

A. Yes.

Q. I don't recall your showing any documents where Cougar advised FDA that prednisone has an anti-cancer effect, did you?

A. I -- could you restate your question.

Q. Let me ask you it more simply.

You are aware that Cougar represented to the FDA that prednisone may have modest anti-tumor effects, correct?

A. In my review of the data that I have reviewed, I have not seen any evidence where Cougar has represented to the FDA regarding any anti-cancer effect of prednisone.

Q. All right. Let's take a look at your own expert report. I want to direct your attention to your own expert report.

THE COURT: In my notebook, I have a rebuttal report and a supplemental. Which one are you talking about?

MR. REIN: Right. Sorry for the delay, Your Honor.
THE COURT: It's okay.
MR. REIN: I'm trying to figure out which of the two reports it's in.
Here we are.
May I approach, Your Honor?
THE COURT: Sure.
MR. REIN: Actually --
THE COURT: But just tell me which one you're talking about.
MR. REIN: Do you have rebuttal expert report on infringement?
THE COURT: Yes I do.
BY MR. REIN:
Q. Do you have it, Doctor, in front of you?
THE COURT: If you've got the black notebook, it's the first item in the black notebook.
BY MR. REIN:
Q. And can you turn to the first item in the black notebook, please.
A. Are you talking about this binder or --
Q. Yes. Yes, sir.
A. Okay. I have the expert report, yes.
THE COURT: For the record, mine is marked Defendants' DTX 1548.

MR. REIN: Correct.

THE COURT: Go ahead.

BY MR. REIN:

Q. Dr. Nagaich, turn to Paragraph 185.

This is from your own rebuttal expert report, correct?

A. Right.

Q. There you reference at the bottom of page 64 that Cougar could only represent to the FDA that prednisone may have modest anti-tumor effects.

Do you see that?

A. Right. In the paragraph states: Cougar justified co-administration of prednisone?

Is that the paragraph?

Q. Yes, the bottom of the first page, paragraph 185.

A. Yes, I -- I write that.

Q. Right. So you were aware that Cougar represented to the FDA that prednisone may have modest anti-tumor effects, correct?

A. Yeah, that's what I wrote, so I must have been aware.

Q. Okay.

MR. REIN: Thank you. I pass the witness.

THE COURT: Whenever you're ready.

(REDIRECT EXAMINATION)

BY MR. WONG:

Q. Hi. All right. Let's just start --

MR. WHITE: One housekeeping question, Your Honor.

THE COURT: Sure.

MR. WONG: That first unmarked exhibit, did you actually mark that in the record?

MR. REIN: I was going to suggest that we do give it an exhibit number since it doesn't have one. And I want to know what the next unused exhibit number is. I understand now it's 459, and I would suggest we mark it as Exhibit PTX 459.

THE COURT: The literature references?

MR. REIN: Yes.

THE COURT: That one? That's PTX -- sorry?

MR. REIN: 459.

THE COURT: 459. And we already have PTX 074 on the other, right?

MR. REIN: I believe that's correct -- yes, Your Honor.

(Plaintiffs' Exhibits PTX 074 and PTX 459 marked for identification.)

MR. WONG: Thank you.

Can we put PTX 459 up on the screen, please.

BY MR. WONG:

Q. Doctor, do you recall counsel directing your attention to

this document, the clinical summary, and there are literature references here?

Do you see that?

A. Yes.

Q. I guess counsel's point was that this is -- this is some indication that scientific articles were, in fact, submitted with the NDA for Zytiga®.

Do you see that?

A. Yeah.

Q. Is that your understanding?

A. Scientific -- I mean, they can be referenced in an IND or NDA, but they're not submitted.

Q. Sure. So -- but counsel never showed you the date of this document, right?

So can we look at the bottom left-hand corner.

Do you see that?

It says: Status approved.

Right?

A. Right.

Q. Date: June 4 -- 4 June 2012, right?

A. That's right.

Q. So does this indicate -- this must indicate that this document was submitted to FDA after Zytiga®'s first approval in 2011, correct? Is that how you would understand that?

A. Could you...

Q. This document is dated 2012 right?
A. Yes.
Q. This document must have been submitted to FDA after FDA already approved Zytiga® in 2011, right?
A. Absolutely. Yes.
Q. All right. So FDA could not have relied on these references, even if it chose to, to approve Zytiga® in 2011?
MR. REIN: Your Honor, I object to his leading his own witness.
THE COURT: Yes, you are leading a bit. Let's take it one step at a time --
MR. WONG: Sure. Sure.
THE COURT: -- and make sure it's the witness who's testifying.
MR. WONG: Sure. We'll slow down.
BY MR. WONG:
Q. So what's the date of this document as you see it?
A. 4 June 2012.
Q. Could this document have been -- and the references relied -- and the references listed here, could they have been relied on by FDA in approving Zytiga® in its first approval in 2011?
A. No.
Q. Now, do you recall counsel also suggesting that in certain hypothetical situations, FDA might have possibly looked at

phase II studies in the Zytiga® NDA as to -- as a basis for approving the indication? Do you recall that conversation between you and counsel?

A. Yes.

Q. All right. Now, let's just stick to the facts as to what actually -- FDA actually did.

Did you see anything in the record, the actual record that you reviewed, what actually happened, to support Janssen's counsel's suggestion that the phase II studies were relied on to support the approval of prednisone for anti-cancer efficacy?

A. I have not seen any evidence to that.

Q. Now, if FDA looked to the phase II studies to see if prednisone had anti-cancer efficacy, would you expect FDA to say this in at least one approval document?

A. Absolutely. Yes.

Q. And based on your review, did they ever say this?

A. No.

Q. All right. At the beginning of cross, counsel asked you about the prednisone monotherapy label.

Do you recall that?

A. Yes.

Q. All right. Just want to clear something up.

MR. WONG: Can we go to JTX 8125.

BY MR. WONG:

Q. Now, when counsel showed you this, he referred you to the

indications, right?

And we reviewed this on direct, so let's go to pages 2 and 3.

Do you remember this?

A. Yes.

Q. Now, counsel asked you questions about the neoplastic diseases on page 3.

Do you remember that?

A. Yes.

Q. He never asked you about the endocrine indication that we discussed this morning on page 2, right?

So let's look at this again for the Court, what's listed here under endocrine disorders.

For the endocrine indication, does it list -- does it say that adrenocortical insufficiency is an approved use of prednisone monotherapy?

A. Yes, it is the approved use for that.

Q. And going back to the Zytiga® label.

MR. WONG: Can we have that DTX 1580. Let's go to the warnings and precautions section. I believe on page 4, let's try page 4. Get the whole thing, right?

BY MR. WONG:

Q. And we talked about this this morning as well, right?

A. Yes.

Q. 5.2 talks about specifically adrenocortical insufficiency,

right?
A. Right.
Q. Okay. So the use of prednisone to treat Zytiga® side effects would be in line -- on label with the approved indication for prednisone monotherapy, would you agree?
A. Could you -- could you state your question again.
Q. Sure.
So when -- like you testified this morning, what does 5.2 explain in the warnings and precautions section as to the role of prednisone?
A. That the role of prednisone is for the side effect of Zytiga® administration for the adrenal insufficiency.
Q. So when a doctor prescribes Zytiga® and prednisone, the prednisone is being used to address adrenocortical insufficiency in line with its monotherapy indication, would you agree?
A. In line with its approved use as a -- for adrenal insufficiency, yes.
Q. Thank you.
And let's stick with the warnings and precautions section. Do you recall counsel asking you about this co-administration section -- sentence?
A. Yes.
Q. That was removed from the 2018 Zytiga® label?
A. Right.

Q. Right. So I think there was a suggestion that counsel made that FDA thought it's no longer needed in this section. Even if this sentence is removed, does the warnings and precautions section and the label as a whole still describe that the role of prednisone is to treat the side effects of Zytiga®?
A. Yes.
Q. So is it necessary to have the co-administration section in the label in order to know that the role of prednisone is for safe -- side effects of Zytiga®?
A. It is not necessary.
Q. Finally, did any of counsel's questions on cross change your mind as to the scope of FDA's approval of Zytiga®?
A. No.
Q. Okay. Now, Doctor, at the end of the day, after reviewing all the evidence that you looked at, did FDA approve the use of prednisone for anti-cancer effects in combination with Zytiga®?
A. No, not at all. FDA has not approved prednisone as an anti-cancer in combination with Zytiga®.
Q. Okay. And -- and you said on direct you reviewed the regulations. Do you remember that?
Do you remember reviewing the FDA approval regulations?
A. Yes.
Q. And I think you testified that the clinical trials

informed the scope of the indication per those regulations?
A. Yes.
Q. So can any -- either of 301 or 302, the phase III trials, can any of those provide substantial evidence of effectiveness of prednisone when used in combination with Zytiga®?
A. No.
Q. Lastly, sir, I just want to talk about this suggestion of modest anti-tumor activity that is -- that was mentioned in the NDA.
A. Right.
MR. WONG: Let's go to DTX 1328. I believe it's in your binder. Your Honor, I think it is in your binder as well.
BY MR. WONG:
Q. Let's start. This is part of the abiraterone NDA. Do you recognize that?
A. Yes.
Q. And what -- if you look at the right-hand corner, what does that say?
A. This is a type C meeting information package for -- for the -- for Zytiga®.
Q. All right. And was this submitted -- is this an FDA document, or was this Janssen submitting it to FDA?
A. This is a Janssen's document submitting it to the FDA.
MR. WONG: Okay. So let's go to page 32 of the document.

BY MR. WONG:
Q. There's a section here that says Rationale for Comparator Arms. Do you see that?
A. That's right.
Q. Do you see on the bottom paragraph?
A. Yes.
Q. Do you see in the bottom paragraph there's a sentence that says: Glucocorticoids have modest anti-tumor activity and palliative effects in CRPC.
Do you see that sentence?
A. Yes, I see that.
Q. And then I think there's -- it goes on to explain?
A. Right.
Q. And there's a citation to Tannock 1996. Do you see that?
A. Right.
Q. And --
A. It says: Two prospective phase III studies have documented the safety and palliative benefit of prednisone.
MR. WONG: And it spills over to the next page. Can we put the next page side by side.
BY MR. WONG:
Q. On the next page there's another reference to Fossa 2001. Do you see that?
A. Yes.
Q. So the Tannock 1996 paper and the Fossa 2001 paper were

available to the public prior to 2006, would you agree?
A. Right.
Q. I want to focus on what Janssen says in the last sentence of this paragraph.
MR. WONG: Can we see that? Can we scroll down a little bit.
BY MR. WONG:
Q. Again, this is Janssen's document; is that right? This is what Janssen is telling the FDA?
A. Right.
Q. All right. Can you read the last sentence, please.
A. Yes. It says: There is no known relationship between the dose/regimen of glucocorticoid and observed anti-tumor activity in CRPC.
MR. WONG: Thanks. No further questions.
THE COURT: Anything further?
All right. You may step down, sir.
Give me one moment.
(Discussion held off the record.)
MS. BLOODWORTH: Your Honor.
THE COURT: One moment, please.
Yes.
MS. BLOODWORTH: I was going to request a quick bio break.
THE COURT: I was going to propose the same thing. I

have a matter I have to deal with briefly. Let's take a 15-minute break right now.

MS. BLOODWORTH: Thank you very much.

(Recess taken 3:10 p.m. through 3:30 p.m.)

THE COURT: Are we about ready?

MR. SWANSON: Yes, Your Honor. Your Honor, defendants' next witness is Dr. Ian McKeague.

THE DEPUTY CLERK: Why is the screen like that?

MR. SWANSON: It went like that before the break.

THE DEPUTY CLERK: I'll turn it off.

THE COURT: That's not good.

There you go.

THE DEPUTY CLERK: Left hand on the Bible, raise your right hand.

IAN McKEAGUE, DEFENDANTS' WITNESS, SWORN

THE WITNESS: Yes.

THE DEPUTY CLERK: Keep your voice up. State your name for the record and spell it, please.

THE WITNESS: Ian McKeague, I-a-n, M-c-K-e-a-g-u-e.

THE DEPUTY CLERK: Thank you, sir.

THE COURT: Introduce yourself and proceed whenever you're ready.

MR. SWANSON: Thank you, Your Honor. Robert Swanson, from Perkins Coie, on behalf of the Mylan defendants, and I will be examining Dr. McKeague behalf of all the defendants.

THE COURT: Okay.

(VOIR DIRE EXAMINATION)

BY MR. SWANSON:

Q. Good afternoon, Dr. McKeague.

Have you been retained as an expert witness in this case?

A. Yes.

Q. And were you retained by all of the defendants in this case except for Amerigen?

A. That's correct.

Q. What is your area of expertise?

A. Biostatistics, which includes statistical analysis of clinical trial data and the design of clinical trial.

Q. And what is biostatistics?

A. Biostatistics is the field in which biomedical data are obtained, first through clinical trials, for example, and then analyzed to extract information from those data and reach conclusions.

Q. Have you prepared a PowerPoint presentation to assist the Court with your testimony here today?

A. Yes.

Q. Is that PowerPoint what is currently projected up on the screen as DDX 2300?

A. Yes.

Q. Let's start with your qualifications. Can you please

describe your educational background for the Court.
A. Yes. I have bachelor's and master's degrees from University of Cambridge 1975. I have a master's -- another master's degree in mathematics, University of Cambridge. And a Ph.D. in statistics from University of North Carolina Chapel Hill in 1980.
Q. And what did you do after receiving your Ph.D.?
A. So I took up a position as an assistant professor at Florida State University, and I was promoted through the ranks. I served a term as chair of the department of statistics. I was a named professor. And then in 2004 Columbia recruited me, and I'm currently a professor of biostatistics at Columbia.
Q. Do you speak at symposia and conferences?
A. I do very regularly.
Q. Could you please describe just a couple of these on the screen that are most relevant to your testimony today.
A. Well, yes. So I regularly speak on clinical trial analysis and design. For example, the Fourth International Symposium on the Evaluation of Clinical Trial Methodologies in Beijing in 2011, I was a keynote speaker. Another example is very recently I was an invited speaker at the International Biostatistical Association annual meeting in Hyderabad; that was in December of 2017.
Q. Could you now tell the Court about the research you've done in your career.

A. Yes. My research career spans almost 40 years of teaching and research experience in statistics and biostatistics. I'm a named author on over 120 peer-reviewed publications.

Q. What about editorial positions on journals, have you held any of those?

A. Yes, I've done extensive service, editorial work. They're here. Here you see a list of some of the journals that I've served. I've served on the editorial boards: Statistical Science currently; Journal of the American Statistical Association, currently; International Journal of Biostatistics; Journal of Statistical Inference for Stochastic Processes. And I have also served on the Annals of Statistics editorial board.

Q. Have you served on any national or international committees?

A. Yes, many. I've served on -- here's a list of the various committees I've served on. The Institute of Mathematical Statistics is an international stat -- the premier society for mathematical statistics, and I've served on their fellows committee. I served on the American Statistical Association awards committee of various types. And the National Science Foundation, I've served on many of their review panels for screening grant proposals and other special panels, special meetings panels and the other panels you see there, which were National Science Foundation.

Q. Dr. McKeague, have you received any professional honors?

A. I have. I'm a fellow of the Institute of Mathematical Statistics as well as the American Statistical Association. I have received various honors, professional honors from Florida State University, including a named professor award, professional -- professional excellence award, and the graduate teaching award.

Q. Do you have experience in clinical trial design?

A. Yes. Well, I teach methodology of statistics, of course, and with that includes clinical trial design and the analysis of data from clinical trials. And it's also a very significant part of my research, probably a third of my papers in some way related to that.

Q. Do you do any consulting on clinical trial design?

A. Yes. So I do consulting -- well, so within Columbia I would call them collaborations on various trials and studies, longitudinal studies. I have also done extensive consulting for biopharmaceutical companies and also some non-profit research institutions. And so I've had experience really looking at all stages of clinical trials from design to data analysis.

Q. Do you routinely publish on survival data?

A. Yes. I think I mentioned that probably a third of my papers have something to do with survival data.

MR. SWANSON: Your Honor, defendants offer Dr. Ian McKeague as an expert on the subject matter of statistics,

including biostatistics, clinical trial design, and statistical analysis of clinical trial results.

THE COURT: Sorry, say the third one again.

MR. SWANSON: I'm sorry. Clinical trial results is the third. So biostatistics, clinical trial design, and statistical analysis of clinical trial results.

THE COURT: Okay. Any objection?

MR. REIN: We have no objection, Your Honor.

THE COURT: As has been the case all along the with others, Dr. McKeague is obviously well-credentialed and qualified to offer opinion testimony in these areas, and I accept him as an opinion witness.

Proceed.

MR. SWANSON: Thank you, your Honor.

(DIRECT EXAMINATION)

BY MR. SWANSON:

Q. Did you submit expert reports in this case, Dr. McKeague?

A. Yes, I did.

Q. Were those expert reports two responsive reports, one on non-infringement and one on invalidity, and a supplemental report?

A. That's correct.

Q. Did you also submit an expert declaration in the Mylan and Wockhardt inter partes review proceedings at the Patent Trial and Appeal Board?

A. Yes.
Q. Have you reviewed the '438 patent?
A. Yes.
MR. SWANSON: Now moving to DDX 2300.12.
BY MR. SWANSON:
Q. What is on this slide?
A. Here you see Claim 1 of the '438 patent.
Q. Have you reviewed all claims of the '438 patent?
A. Yes.
Q. Do you know what a claim construction is?
A. Yes.
Q. Are you familiar with the Court's claim constructions in this case?
A. Yes.
Q. What is your understanding of the Court's claim constructions in this case?
A. So I understand that the Court has defined the phrase "therapeutically effective amount" in this case as in the wording of the -- claim 1 of the patent to mean "an amount effective for treating cancer."
And I've also -- understand that the claim construction defines treatment or treating as "the eradication, removal, modification, management, or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer."

Q. For simplicity is it okay if I refer to the definition of "treatment" and "treating" in terms of "anti-cancer effects"?
A. Yes.
Q. How do those claim constructions fit into the context of Claim 1?
A. So we see the phrase "treatment" and -- the word "treatment" and the phrase "therapeutically effective amount" and the highlighted phrase there: Therapeutically effective amount of abiraterone acetate or -- we can read on -- and a therapeutically effective amount of prednisone.

So both abiraterone and prednisone must have an anti-cancer effect under the claim of the patent.

Q. Are you familiar with the parties' definitions of the person of ordinary skill in the art?
A. Yes.
Q. And have you read and adopted the definition of the person of ordinary skill in the art that will be presented by defendants' expert Dr. Lipton?
A. Yes.
Q. Could you please read defendants' definition of a person of ordinary skill in the art which you applied into the record.
A. Yes. A POSA in the subject matter of the '438 patent would be: A physician specializing in medical oncology or urology having an M.D. and/or a Ph.D. in pharmacology, biochemistry, or related discipline. Significant practical

experience, for example, five to six years' worth in medical oncology or urology could substitute for the advanced degree. It is understood that the POSA would have access to individuals having expertise in pharmacology, biochemistry, endocrinology, enzymology, and/or molecular biology, and would collaborate with them as necessary.

Q. Have you also reviewed plaintiffs' definition of the person of ordinary skill in the art?

A. Yes.

Q. Do your opinions given in this case depend on whether plaintiffs' or defendants' definition of a person of ordinary skill in the art is applied?

A. They don't depend on that.

Q. So if plaintiffs' definition of a person of ordinary skill in the art were to be applied in this case, would your opinions be the same?

A. Yes.

Q. Dr. McKeague, were you provided a transcript of Dr. Rettig's testimony earlier at trial?

A. Yes.

Q. Did you review that transcript?

A. I did.

Q. Were you also present for the direct infringement portion of Dr. Rettig's direct examination?

A. Yes.

Q. What is your understanding of whether plaintiffs have the burden of proving infringement including direct infringement?
A. My understanding is that plaintiffs do not have -- sorry. The plaintiffs do have the burden of proving direct infringement.
Q. And what do you understand direct infringement to require?
A. I understand that direct infringement requires that someone, a patient or a physician, practice each element of the patent claim.
Q. And do you also understand that Dr. Rettig will later provide certain opinions on alleged unexpected results of the '438 patent?
A. Yes.
Q. What do you understand is required to show an unexpected result?
A. To show an unexpected result, the alleged invention must produce benefits that were unexpected in light of the prior art from the viewpoint of a person of ordinary skill in the art at the priority date of the patent.
Q. Do you understand that Dr. Rettig's opinions on alleged unexpected results will rely on largely identical underlying evidence as his opinion on direct infringement?
A. Yes, I understand that.
Q. For simplicity's sake, I will refer to Dr. Rettig's opinions on alleged direct infringement and alleged unexpected

results together as his opinions on prednisone's alleged anti-cancer effect.

Do you agree with Dr. Rettig's opinions on prednisone's alleged anti-cancer effect?

A. I do not.

Q. Would you please summarize the opinions you will provide today.

A. So my opinion's that Janssen has not demonstrated that prednisone has an anti-cancer efficacy when used in combination with abiraterone acetate.

Q. What does that opinion mean in terms of direct infringement and unexpected results?

A. So that means there's no direct infringement of the patent, and it also means no unexpected results.

Q. Let's go through each one of Dr. Rettig's arguments individually. What is his first argument?

A. So his first argument is based on looking at selected patients from phase I, phase II studies, then looking at the dexamethasone extension study part of those studies.

Q. And why do you disagree with Dr. Rettig's first argument?

A. Because he selects some patients. He doesn't analyze all the data. His argument is anecdotal, so you can't base such an argument on anecdotes. There's no statistical analysis being formed.

Q. What is Dr. Rettig's second argument?

A. So his second argument is a cross-study comparison of two early-phase studies and, yes, that's what his argument is based on.

Q. And why do you disagree with Dr. Rettig's second argument?

A. Well, although these two studies are published, a cross-study comparison has not been published. This is purely Dr. Rettig speculating on the basis of this cross-study comparison.

And it's -- in my view, it's an improper cross-study comparison. At least Dr. Rettig hasn't provided the requisite statistical analysis to do the cross-study comparison.

Q. And what is Dr. Rettig's third argument?

A. His third argument is based on phase III studies with survival outcomes.

Q. And why do you disagree with Dr. Rettig's third argument?

A. Well, his third argument is based on looking at these phase III studies, but unfortunately, prednisone is in both arms of all these studies he looks at. So they were not designed to test or assess whether prednisone has an anti-cancer effect.

Q. Okay. Let's go through each of Dr. Rettig's opinions in turn and starting with the first argument, which discusses the clinical study with the dexamethasone data.

So before we get to Dr. Rettig's argument, let's go over some statistical principles.

What is statistical analysis?

A. So statistical analysis is the use of certain calculations, given the data, to assess and test whether a hypothesis of interest can be established and, more generally, to draw inference about a population.

Q. I will let you have your drink of water.

A. Yes. Right.

Q. Dr. McKeague, why are calculations and tests needed to draw inferences from data?

A. Because data typically contain a lot of variation that may not be indicative of the effect that's trying to be established. So we need to be able to discriminate random variation, random pattern in the data from a real pattern that we may be interested in.

Q. Could you please provide an example to illustrate this concept.

A. So say we toss a coin three times. If it's a fair coin, even, we could just -- we very likely could get three heads in a row purely because of randomness. That's not an indication, necessarily, that it's a biased coin. Of course, a biased coin could cause three heads in a row. So we need to discriminate between the notion of random variation and the real effect, in this case biased coin.

Q. What happens if you flip 100 coins and then they all come up heads?

A. Yeah. So in the case of 100 coins observing 100 heads is, of course, enormous -- enormous evidence to indicate that this is indeed a biased coin because it is very unlikely that a fair coin would turn up 100 times heads at random.
Q. How would you assess the weight of the evidence in this example?
A. We would actually carry out a formal statistical test to test whether, indeed, the coin is biased, to assess the evidence and do a formal test.
Q. So in light of that, what is a hypothesis test?
A. So a hypothesis test is, it's a -- so we're examining the data. We formulated a hypothesis, and we like to use the data to validate or find evidence for that hypothesis that we've made.
Q. And in statistics, what does power mean?
A. Power is a measure of the strength or accuracy that we can actually test the hypothesis based on a data set we might collect.
Q. Finally, what is statistical significance?
A. So statistical significance is a measure of actually the power of the data to confirm the hypothesis that we're trying to test.
Q. Let's now move on to discuss the COU-AA-001 study, which I will refer to as the 001 study for short.
THE COURT: I'm sorry. Could I just ask a naive

question.

THE WITNESS: Yes.

THE COURT: Statistical significance, there's a proverbial P-value that corresponds to that.

THE WITNESS: Yes.

THE COURT: But in this area where the cost of a mistake is someone's health or life, is there a different test of statistical significance?

THE WITNESS: Well, you have a good point. You -- in the case of where a life is at stake, you might require a very much more stringent level of statistical significance than, say, a .05 level, which is a --

THE COURT: Yes. A 1-in-20 chance it could be chance. But what I'm saying is, does that alter -- you might require more as a practical matter --

THE WITNESS: Yes.

THE COURT: Does it alter the statistical analysis, is what I'm saying.

THE WITNESS: No, it doesn't. The P-value -- as long as the statistical analysis is done in a careful and diligent way and accurately, then the P-value can speak for itself as a summary of the evidence in the data.

THE COURT: I understand. Thank you.

BY MR. SWANSON:

Q. And so moving to the 001 study, do you understand that

Dr. Rettig's argument on the dexamethasone extension study involves the 001 study?
A. Yes.
Q. And I'll refer you to DDX 2300.25, which shows JTX 8083. What does this reference?
A. This is the Attard 2008 paper reporting on the phase I portion of the 001 study.
Q. Have you reviewed the Attard 2008 publication in forming your opinions?
A. Yes.
Q. And referring now to DDX 2300.26, which shows JTX 8086. What is this reference?
A. This is a subsequent paper on the 001 study reporting phase I -- a little bit of phase I, phase II results as well as something on the extension study, the dexamethasone extension.
Q. And can I refer to this publication as the Attard 2009 paper?
A. Yes.
Q. Have you reviewed the Attard 2009 paper in forming your opinions?
A. Yes.
Q. Could you please describe the design of the 001 study?
A. Yes. So it's a phase I/II study. There was a single arm. The patient population was chemo-naive patients. There was a drug escalation phase, as there typically is in a phase I

trial. Then a 1000-milligram abiraterone acetate in the phase II portion of the trial.

And then in the extension phase that I mentioned, patients were on 1000 milligrams of abiraterone and .5 milligrams of dexamethasone per day. And the outcome that was tracked on the patients in the trial was the PSA measure, the prostate-specific antigen measure.

Q. Did 001 study measure survival?

A. It did not, no.

Q. What is the role of studies like the 001 study in scientific research?

A. Well, they're dose-finding as well as safety. Primarily, dose-finding, safety. Possibly they can suggest some efficacy, but the aim is primarily dosing and safety issues.

Q. And on the spectrum of evidence from no data at all to phase III statistically significant results for proving or disproving the reversal of resistance hypothesis, where does the extension data from the 001 study fall?

A. So it falls on perhaps a glimmer of inspiration for those people who would believe the reversal of resistance hypothesis. They have this extension data, and they present a little fragment anecdote. And that may well inspire some scientists to actually go out and try and prove this speculative hypothesis of reversal resistance.

Q. Let's talk now about Dr. Rettig's reversal resistance

argument using the dexamethasone data. Could you explain why you disagree with Dr. Rettig's argument.

A. Well, actually, I already mentioned he has an anecdote. He looks at particular patients out of 30 patients. And so an anecdotal or selection of patients cannot actually produce evidence. It can tell you something about those patients he selected, and maybe it tells you something about the biases of the choice in the selection. But it's not actually a statistical analysis or a statistical test.

Q. Let's look at a couple of those patients.

MR. SWANSON: Could we please pull up the two figures at JTX 8083.11.

BY MR. SWANSON:

Q. Dr. McKeague, do you understand that these figures appear in the Attard 2008 paper?

A. Actually, I don't think they're in the text of the paper itself. They're in -- on a web supplement. They appear, yeah, almost without explanation, I understand, in this web supplement.

Q. What does it tell you as someone who served as an editor and peer reviewer for prestige academic journals that these two figures appeared in a web supplement?

A. Yeah. So if the figures are not discussed in-depth and analyzed in the body of the paper, then it's essentially material that -- it's extra material. Probably very likely --

or if at all even -- peer reviewed.

So usually there's no limitation on space in a web supplement. There's, of course, very strict page limitation because journal space is very precious.

So authors are given the option of putting as much material as they wish into a supplement. Often it's actually requested by the referees that they put all supplementary data into the web supplement.

Unfortunately, here we only see two sort of cherry-picked patients put into the web supplement. And the motivation for doing so, I am -- is unknown to me. But that's what we see in the web appendix.

MR. REIN: Your Honor, I know this is a bench trial, but this testimony is not in his expert report. He doesn't have license to go beyond his expert report.

There's no testimony in his expert report about this being in an appendix and the meaning of that. I don't know that he's an expert on journal publications in this space either.

I thought he was here to testify as a statistician.

THE COURT: I don't care a lot about where it was in terms of the text of the article. But let's talk about your objections to what's being done here in terms of statistics, and that's really what I'm interested in. So let's concentrate on that.

As for anybody's motives for doing this or where it appeared in the article, I'm not interested. Okay?

MR. SWANSON: Thank you, Your Honor. We're going straight to the statistics now.

BY MR. SWANSON:

Q. Dr. McKeague, do you understand that these are two of the patients that plaintiffs point to as showing reversal of resistance?

A. Yes. I understand there's a -- in the supplement, there is a little title saying "reversal of resistance," I think, for these patients.

Q. Dr. McKeague, you're not an oncologist, right?

A. No.

Q. But as a biostatistician, how often do you consider clinical study data such as that shown on the slide?

A. So I very often consider longitudinal data in a general sense of where subjects are tracked through time longitudinally, and this is exactly that type of data for PSA, tracks through time.

Q. Are biostatisticians routinely part of a clinical study team in studies like these?

A. Yes, absolutely.

Q. Why is that?

A. Because biostatisticians need to be there when the study is designed to make sure that the data collected in the study

can be deemed reliable. And then as the data begins coming in, there's, of course, a data-monitoring committee. And then statisticians will be involved in the analysis of the data and eventually the publication of the results.

Q. Are you aware that Dr. de Bono, one of the inventors of the '438 patent, testified in this trial that some variation in PSA is typical of PSA testing?

A. Yes, I am aware. I saw his testimony on that.

Q. Are you also aware that Dr. de Bono testified that there is variability in the assays used to measure PSA?

A. Yes, I understand that.

Q. Could you please describe whether there is any variability in these two figures that illustrates the danger of cherry-picking data?

A. Yes. So -- well, for one thing, just comparing the two, they look very different. The trace plots look rather -- there are these sudden jumps and so on.

And you could conclude various things. You could discuss or try to interpret these jumps. But there is, of course, a lot of variability.

One thing you might notice, if you just look at, for example, the second patient, patient B, you see from the start of the abiraterone that there's a rather -- there's a little drop; then there's an increase. So that patient has progressed immediately -- the PSA progression immediately on abiraterone.

So if you just selected that patient, you would say, Well, this patient really shouldn't be on abiraterone. It's not doing good for this -- well for this patient, so abiraterone shouldn't be used if you follow this principal of just cherry-picking a patient.

But, of course, there's a lot of other patients we should look at. So patient A, for example, because of this -- there's a sudden drop in patient A's PSA level -- this has been remarked on before by other experts. So there we get quite the contrary impression, that abiraterone is doing -- is helping this patient.

So there are these sudden drops, sudden statistical variations. And this is the danger of cherry-picking individual subjects to highlight or try and make an argument. You really need to look at all the data.

THE COURT: Mr. Rein.

MR. REIN: Yes, Your Honor. Again, that level of detail is just not in his expert report. I mean, he's a statistician. He's not an expert in oncology or the like. And the only thing I think that's in his expert report that relates to that answer is the word "cherry-picking."

There's no similar explanation given, and he wasn't deposed on this as a consequence.

THE COURT: You won't be surprised to learn I have not read his expert report or reviewed the deposition, but is

Mr. Rein correct? This was not gone into?

MR. SWANSON: So Dr. McKeague absolutely considered the Attard 2008 paper. He presented the argument in his expert reports that they represent cherry-picking of data and that there's variability in the data set. I suppose these exact figures picture-wise are not in the report, but he certainly makes the same arguments that he's presenting.

THE COURT: Well, did he address figure A1.

MR. SWANSON: He expressly addressed the cherry-picking of data, which, you know, while I said these exact figures are not copied and pasted in his report, he is responding to Dr. Rettig, these figures were copied and pasted in Dr. Rettig's report.

And Dr. McKeague responded by saying this is cherry-picking of data.

THE COURT: I am going to permit it. Once again, this isn't stuff we have to sift through before a jury hears it. I will hear it.

I understand that from a statistical point of view you're talking about what is sometimes called the "N equals 1" problem. And I understand that you're talking about the dangers of that. And I will take it for that.

I also will give an expert some latitude to talk about the prior testimony in the case, which he's heard and we've certainly heard about this. So I will permit it.

MR. SWANSON: Thank you, Your Honor.

BY MR. SWANSON:

Q. Dr. McKeague, how often do patterns seemingly appear in data but that are the product of random chance?

A. Yes. This is one thing we have to be very careful about as statisticians. We can't just -- the coincidences can happen.

For example, in a room of just 23 people, there's more than even odds that two people will have the same birthday. That's a coincidence, but it shows you don't need many people in a room for that to happen. So it's surprising.

So we have to be able to exclude coincidences.

Another coincidence that might surprise you is that within the last ten years, two people can -- sorry -- one person can win two lotteries. That happens on average about once every ten years.

So, again, coincidence and surprising.

So you can't just sort of cherry-pick data and find a coincidence and say, Well, that's evidence.

No, it's not. It can be explained just by variation.

We talked about the problem of distinguishing variation from a real effect. So coincidence can be a phenomenon of just a random variation.

Q. Do you understand that plaintiffs have asserted that the patients in the 001 study served as their own controls?

A. I've heard that statement, yes.
Q. Can statistical tests be performed on data from patients that served as their own controls to determine whether an effect is likely real versus the product of random chance?
A. Yes. It's a challenging enterprise. You have to build sophisticated modeling to do that because you can appreciate, there's crossover effects between changes in treatment.

And here we see very complicated treatment patterns and very complicated longitudinal data. There's lots of variation. All that needs to be modeled in some sense to have a real valid statistical study and actually evaluate the evidence.

Q. Did Attard 2008 perform any statistical analysis to determine whether patient A's data support the reversal of resistance hypothesis?
A. No.
Q. Did Dr. Rettig perform any statistical analysis to determine whether patient A's data support the reversal of resistance hypothesis?
A. Yes.
Q. With respect to patient B, did Attard 2008 perform any statistical analysis to determine whether patient B's data support the reversal of resistance hypothesis?
A. None.
Q. Did Dr. Rettig perform any statistical analysis to

determine whether patient B's data support the reversal of resistance hypothesis?
A. No.
Q. Based on those facts, can it be determined whether the alleged reversal of resistance in these two patients was a real effect or simply random variation?
A. It can't be determined.
Q. Why is that?
A. Because this is just -- for the reasons I've just given -- this is anecdotal. No statistical analysis was performed using all the data. And -- so you can't reach a conclusion -- you can't draw the inference of -- that there was reversal of resistance.
Q. So can these two figures from Attard 2008 provide any reliable evidence of an anti-cancer effect of prednisone when given with abiraterone acetate?
A. They cannot.
THE COURT: I'm sorry. Just let me make sure I understood what the question was. Do you mean standing alone?
MR. SWANSON: In combination with abiraterone acetate.
THE COURT: No, no, no, I mean the two --
MR. SWANSON: Oh, I'm sorry. Yeah, so standing --
THE COURT: Two patients?
MR. SWANSON: Yes. For now, standing alone, these

two --

THE COURT: This isn't the whole paper. I mean, there's --

MR. SWANSON: Correct.

THE COURT: There's more in there.

MR. SWANSON: We're moving right to that next.

So next, could we please pull up the figure at JTX 8086.8.

BY MR. SWANSON:

Q. You reviewed the Attard 2009 paper, correct?

A. Yes.

Q. You rendered opinions on the Attard 2009 paper in this case?

A. I did.

Q. Do you understand that this figure appears in the Attard 2009 paper?

A. Yes.

Q. And so does that mean -- excuse me.

Do you understand that this is a figure plaintiffs point to as showing reversal of resistance?

A. Yes, I understand that they have pointed to this.

Q. So let's walk through this figure so that it's clear what this is actually depicting. Let's start with what the bars mean.

MR. SWANSON: Mr. Russell, if you could blow up the

text that's just below the figure.
BY MR. SWANSON:
Q. Dr. McKeague, could you explain what these bars are showing?
A. So the bars represent different patients, each different patient. The height of the bar or depth of the bar represents the maximal prostate-specific, PSA, change after addition of dexamethasone to abiraterone acetate.

So the patients were on the abiraterone acetate at some point. They go from -- they go into the dexamethasone, and this is the percentage change from their baseline -- the value of PSA when they go on the dexamethasone. Yeah, so that's what it says.

It is important -- and it's also -- there's a time consideration here starting from the beginning of the dexamethasone through any point beyond 12 weeks. So it's after 12 weeks, and we're looking at the maximal change, maximal is important to note.

MR. REIN: Your Honor, I would again note -- first, maybe I should pass up to Your Honor his report. None of this is in his report. There's not this graph. There's no discussion of the graph.

THE COURT: Okay. Well, we can sort this out later. You are going to have some post-trial briefing. You are going to tell me why I shouldn't pay any attention to any of it.

MR. REIN: Sure.
THE COURT: We're going to make our record here so we don't all have to come back and do this again.
MR. REIN: Sure.
THE COURT: Okay.
MR. SWANSON: Thank you, Your Honor.
THE COURT: But that said, if you've got an objection, by all means at least preserve it.
MR. REIN: So objected.
BY MR. SWANSON:
Q. So just to sum up this figure, so these bars are the maximal change in PSA at any single time point after the patients have been on dexamethasone and abiraterone for 12 weeks?
A. Yes, that's correct -- well, really from the start of the dexamethasone here.
Q. And was there any requirement that this maximal change in PSA was durable for any period of time?
A. No. They could have had a very high -- for all we know, they could have had quite a high PSA for quite a while, and then there's some fluctuation or variation in which it drops. And that would be the maximal change. It could be -- it could drop negative, could go positive. But yeah. We don't -- we don't know anything about the average PSA here. It's just the maximal change.

Q. So let's look at how that compares to the primary endpoint of the Attard 2009 study.

MR. SWANSON: Mr. Russell, could we please have JTX 8086.2. And specifically the right-hand column there under the study heading, we're going to look at lines 4 through 6. Beginning with: The primary endpoint.

THE WITNESS: Yes.

BY MR. SWANSON:

Q. So, Dr. McKeague, what was the primary endpoint in the Attard 2009 study?

A. The primary endpoint was a greater than or equal to 50 percent PSA decline at any time after 12 weeks of treatment confirmed by a second PSA 4 weeks later. So --

Q. And how does the primary endpoint in Attard 2009 differ from the data in the waterfall graph?

A. Because here we see a confirmation by a second PSA; whereas, there's no mention of any confirmation in the waterfall graph.

Q. Turning back to the waterfall plot at JTX 8086.8, do you notice anything else unusual about this figure?

A. Yeah. There's something unusual about the scale and the truncation at the top of the scale. So it looks as though the scale was delimited to a maximum of 25 percent. So you will see that this is sort of the cutoff at 25 percent along a fair number of those bars there.

So those bars could, of course, extended very high. And that's giving actually a kind of misleading, or deceptive even, impression of the results here.

Q. Did Attard 2009 perform any statistical analysis to determine whether these data support the reversal of resistance hypothesis?

A. No, there's no analysis.

Q. Did Dr. Rettig perform any statistical analysis to determine whether these data support the reversal of resistance hypothesis?

A. No, none.

Q. Based on those facts, can it be determined whether the alleged reversal of resistance depicted in this figure was a real effect or simply random variation?

A. It can't be determined.

Q. Why not?

A. Because -- well, first of all, no statistical test was performed on these data; and the other reasons I gave, this truncation problem and also the lack of confirmation of second measurements.

Also, what else? So there's a lot of information in these data actually, the PSA longitudinal data that is sort of crudely summarized in this graphic. And it really -- to do a proper analysis, that would have to be used.

Q. So can the waterfall figure in Attard 2009 provide any

reliable evidence of an anti-cancer effect of prednisone when given with abiraterone acetate?

A. It cannot.

Q. So what do the data Dr. Rettig presented from the dexamethasone extension study tell you about whether prednisone has an anti-cancer effect with abiraterone?

A. They can't provide evidence of the reversal resistance hypothesis. They may provide some inspiration for further -- an idea for further research. But in terms of actual evidence, there's not enough evidence or no evidence actually.

Q. Let's address Dr. Rettig's second argument, which is Dr. Rettig's cross-study comparison. And before we proceed with his specific argument, let's get a little more background on statistics.

So you talked earlier about statistical significance and using statistics to make inferences about a set of data.

What is a point estimate?

A. A point estimate is obtained from a sample or hopefully a random sample of individuals, say, from a population. And, for example, say we're interested in estimating the average height of the population. We may take a sample of 12 individuals. There we see it. We may find that the average height in that sample is 5 feet 10. We can use that as an estimate of the population mean height.

Q. What is a confidence interval?

A. A confidence interval is a way of quantifying the precision of a point estimate. It gives us a region around the point estimate that we may have a certain degree of confidence, in this case, say, 95 percent confidence that the true average height in the population falls between limits in this picture, say, 5 feet 6 to 6 feet 2.

Q. Is there a standard level of confidence used in the scientific literature?

A. Yes. For reporting purposes, often -- well, almost invariably, 95 percent is used as -- just as a default.

Q. Dr. Rettig performed a cross-study comparison. What is a cross-study comparison?

A. A cross-study comparison is comparison of the data or results across two different studies. Even more than two studies. It can be multiple studies.

Q. And in terms of drawing conclusions from a single study versus comparing data across studies, which is preferable?

A. Well, it's always preferable to have a single study because all the analysis is done on the single data set. The problem with cross-study comparisons is the data were collected from two different populations, patient populations. And you need sophisticated methods to assess the differences between those populations, and you can't adjust for them.

Q. Are cross-study comparisons ever appropriate?

A. Yes, they can be appropriate. And they require -- they

require careful analysis and -- but the problem with them is that even though the individual studies may have been published, it's the combination of the two that is challenging. And that needs to be published and peer-reviewed as a separate publication.

Q. You described the 001 study earlier, which is one of the two studies Dr. Rettig compares. Are you also familiar with the COU-AA-002 study, which I will call the 002 study?

A. Yes.

Q. Could you briefly describe the 002 study.

A. This was a phase II study, single arm of chemo -- on a chemo-naive population. The drug treatment was 1000 milligrams of abiraterone plus 10 milligrams of prednisone per day.

Q. Let's turn to Dr. Rettig's argument. And here we're looking at Dr. Rettig's demonstrative, PDX 4.63.

What's your understanding of Dr. Rettig's cross-study comparison argument?

A. So he's putting these two studies, the 001 and 002 here, in the rows and summarizing various things. He has a column about time to PSA progression. And he notes that in the 001 study time, time to PSA progression is 7.5 months. And in the 002 study, it was 16.3 months.

Q. Was Dr. Rettig's cross-study comparison ever published?

A. No.

Q. What is the role of cross-study comparisons like

Dr. Rettig's in scientific research?
A. Well, there is, of course, a great need to compare treatments. And so a cross-study comparison, when carefully done, is certainly publishable if it's -- if there's some new insight obtained.
Q. Is Dr. Rettig's conclusion appropriate from the data?
A. Well, he doesn't perform any statistical analysis or evaluation of this comparison that he makes.
Q. Could you please give me an overview of your major criticisms of Dr. Rettig's analysis.
A. Yes. So he failed to show there's any statistically significant difference in the median time to prostate progression -- to PSA progression. I'm sorry.

So no statistical tests, no analysis. He ignores another Janssen study, Janssen data, I should say, that conflicts with the results of this cross-study comparison.

And so a really major shortcoming is he failed to account for the differences in the study populations across the two studies that he compares.
Q. Let's take your first criticism that Dr. Rettig failed to show a statistically significant difference.

MR. SWANSON: If I could have PDX 4.63 again.

BY MR. SWANSON:
Q. Dr. Rettig says that one point estimate is more than twice the other point estimate. Why can't you conclude that the

median TTPP is more than twice as long on abiraterone and prednisone than just abiraterone alone?

A. Because I talked about the need to quantify the precision or accuracy of a point estimate. And these are just point estimates. So there needs to be something extra to actually see whether that is a significant difference.

Q. Looking at DDX 2300.38, what does this slide depict?

There we go, 2300.38.

A. So this slide depicts some extra information from the paper in the third column there -- in the two papers that we're talking about here, reporting the results of these two studies that he compares.

We see, in fact, that there were 95 percent confidence intervals provided in the papers. And you can see that for the abiraterone treatment, monotherapy, the confidence interval median time to PSA progression ranges from 5.4 to 9.6 months.

In the bottom row of the table, the abiraterone plus prednisone, the median time to PSA progression ranges from 9.2 months and there's no upper limit. It's an infinite upper limit.

Q. Do you have a graphic illustrating the confidence intervals?

A. I do.

Q. Is that graphic displayed as DDX 2300.40?

A. That's correct.
Q. And could you please describe this graphic.
A. So the comparison between the confidence intervals appears here, the abiraterone monotherapy in the top and abiraterone plus prednisone on the bottom. There's an overlap between the confidence intervals, the 95 percent confidence intervals here.
Q. Why does it matter that the confidence intervals overlap?
A. Well, it throws doubt on the possibility that there would be a significant difference here.
Q. Can the conclusion be drawn that there is a significant difference if the confidence intervals overlap?
A. No.
Q. Did you hear Dr. Rettig note that the overlapping confidence intervals was small and maybe six days --
A. I heard him say that.
Q. Does it matter whether the overlap between the two confidence intervals is large or small?
A. No, it doesn't matter for purposes of making a decision, a statistical decision based on an inspection of this.
Q. So bringing it back to Dr. Rettig's argument that the point estimates are different, what is your ultimate conclusion regarding the confidence intervals?
A. So my ultimate conclusion is that Dr. Rettig did not show that a difference in median time to PSA progression between abiraterone acetate plus prednisone and -- versus abiraterone

is statistically significant.
Q. And for those of us in the room who aren't statisticians, can you please explain what that means in terms of Dr. Rettig's argument that these studies show that prednisone has anti-cancer effects when combined with abiraterone acetate?
A. He hasn't provided any evidence to that, to justify that.
Q. Let's now take your second point regarding the cross-study comparison --
THE COURT: Actually, just back up one second.
Expand a little bit on the idea that the size of the overlap doesn't matter. Now, obviously, if they overlap at all, then they could be the same. There could be no difference between them.
THE WITNESS: Yeah.
THE COURT: That's one possible configuration.
Why would not the size of the overlap reflect on the likelihood that they are the same?
THE WITNESS: Well, it's very difficult to assess that. There's no -- you know, these are confidence intervals from two separate studies. That's all we have. We don't have the original data to actually do a proper comparison, at least -- or Dr. Rettig may have had it, but I don't.
All we can do, actually, is just compare these two.
And you're right; it's a small overlap. So that may say, well, maybe that's a little bit encouraging. Maybe

further investigation should be done. There's a hint maybe or this may inspire -- as I said earlier, it may inspire somebody to actually design a more powerful study.

THE COURT: Well, sure. But if, for example, they overlapped completely -- that is, these two -- then we'd be able to say it's quite likely --

THE WITNESS: I would rather put it the other way around. If there was a significant -- if those confidence intervals were well separated, then we would have evidence. I would agree with that.

We are looking for evidence in favor -- so to prove a claim or a hypothesis, you need to -- that needs what's called the alternative hypothesis. So we need -- this is like -- so here we're still under null hypothesis. There's no evidence that we've rejected the so-called null hypothesis.

THE COURT: I understand.

THE WITNESS: Sorry. I am sorry to go into the jargon.

THE COURT: I'm familiar with the jargon.

Go ahead.

BY MR. SWANSON:

Q. Now we're moving to the second point that Dr. Rettig ignored conflicting data. Could you please explain that point a little more.

A. Yes. So there are other Janssen studies that do indeed

conflict in the sense that -- it's the same comparison, actually, yet the median time to PSA progression and the point estimates actually turn out to be identical.

Q. Turning to DDX 2300.43, which shows the table based on DTX 1185.4, which is the Reid 2010 paper, and JTX 8090.3, which is the Danila 2010 paper, did you review the Reid 2010 paper in forming your opinions?

A. I did.

Q. Did you review the Danila 2010 paper in forming your opinions?

A. I did.

Q. Can you please take us through this slide.

A. So yes. So these two papers you just mentioned were the published papers on 003 and 004 studies, respectively. They were in patient population of chemo-refractory patients. And the treatment in the 003 was 1000 milligrams of abiraterone acetate.

In the 004, the patient -- the treatment was -- they were single-arm phase II studies. The treatment was 1000 milligrams of abiraterone acetate with 10 milligrams of prednisone per day. And you see the median time to PSA progression was 5.6 months. It was actually equal in those two.

Q. So what would the confidence intervals look like in this situation?

A. Well, the confidence intervals actually weren't provided in the paper. But the confidence interval contains the point estimate; therefore, those two confidence intervals will have to overlap very significantly, of course.

Q. What does this conflicting data tell you as a biostatistician?

A. Well, it tells me that Dr. Rettig sort of ignored this conflicting information. If he thought his previous cross-study comparison was valid, why not this one? Then this information would be apparently relevant, but he chose to overlook it.

Q. Let's now take your third criticism that Dr. Rettig's cross-study comparison does not control for differences between the study he compares.

THE COURT: Actually, just back up one.

I get it there can be kind of hindsight where you say, Look, this drug worked on 100 percent of the people it worked on.

But would it not be a valid hypothesis that there could be a difference in how this drug works on chemo-refractory patients and chemo-naive patients, and that might be a perfectly valid reason to consider them separately?

THE WITNESS: Well, yes, Your Honor. But I think the patent doesn't refer to chemo naive or chemo refractory. And I think Dr. Rettig's assertions were independent of that.

The reversal of -- my understanding is that the reversal of resistance hypothesis is thought to hold generally.

THE COURT: Okay.

BY MR. SWANSON:

Q. So now moving to your third criticism, that Dr. Rettig's cross-study comparison does not control for differences in the studies he compares, could you please explain your opinion here.

A. Yes. So, now, Dr. Rettig did not actually show much concern about differences between the studies. And certainly it requires very careful attention to do a thorough study to adjust for differences.

You really need to control for those differences in the statistical analysis in some way, and I won't go into detail the techniques that statisticians use to do that. But they should be done because they're from different patient populations.

And the beauty of a randomized trial is that you're selecting the patient from the same population; therefore, any differences can't be because you're selecting from the same population.

And randomization allows you to actually make a much stronger statement, a causal effect in a sense.

So Dr. Rettig didn't do a proper cross-study comparison. He ignored potential differences between the

populations; and, therefore, you cannot actually make a valid conclusion based on his comments.

Q. So now moving to DDX 2300.46 and without going into them quite yet, are these examples of the differences between the 001 and 002 studies that jumped out to you as a biostatistician?

A. Yes.

Q. And now referring to the next slide, what is the difference in median baseline PSA level between the 001 and 002 studies?

A. It's -- in the 001 study, the median baseline PSA level was 110 units. In the 002 study, it was 23 units.

Q. And what is the drop in PSA in patient A of Attard 2008 on dexamethasone and abiraterone?

A. It appears to be -- I can draw it on the picture if you like. So this drop here is about 30 units.

Q. And how do the two numbers compare?

A. So we're comparing 30 units with about 90 units, the difference in the PSA between the Attard and Reid studies.

MR. REIN: Your Honor, I am going to make an objection for the record. This is, again, not in his expert report.

THE COURT: Okay. I understand.

BY MR. SWANSON:

Q. So, Dr. McKeague, is it your understanding that plaintiffs

contend that the difference in median baseline PSA level between the 001 and 002 studies isn't meaningful but that the drop in PSA experienced by patient A of Attard 2008 was an important scientific discovery?

A. Yes, I understand that.

Q. How could a difference in the patient's baseline PSA values have affected the results reported in the two studies?

A. Well, as a biostatistician, I would be very concerned that that would create a difference because the measure being recorded as an outcome measure in the -- in those studies is PSA itself, some -- something depending on PSAs.

So if the baseline PSA is markedly different between the two patient populations in those studies, you have to be very careful about comparing the results.

Q. Does the difference in the number of prior hormonal cancer treatments between the 001 and 002 studies indicate anything to you about the relative sickness of the patients in the 001 and 002 studies?

A. Yes. That would be a concern to me as a biostatistician, so there were -- the median number, prior number of hormonal cancer treatments in the 001 was 3. But in the 002 study, 88 percent of the subjects had only 2 prior hormonal treatments.

So it appears that this is consistent with the PSA as well, that the patients in the 001 study, just based on this

information, appear to be sicker.
Q. How should Dr. Rettig have addressed the difference in baseline PSA between the 001 and 002 studies?
A. So at a minimum, he should have developed a statistical method for carrying out an adjustment to do that. As I say, I won't go into details of how that could be done, but it could have been done.
Q. Let's move to the third and fourth rows of this table. Could you please explain why you've highlighted the differences in number of study center locations between the 001 and 002 studies.
A. Yeah. The 001 study was in the United Kingdom, 1 study center.

The 002 study was in the United States with 5 study centers. I don't know where, but wherever. So in particular, there are some demographic -- I think everybody would agree there are demographic differences between the United Kingdom and the United States. That's possibly a -- that's possibly a significant difference. Differences in diet, for example.

So there are -- again, there are statistical methods to adjust for differences in location and also numbers of study centers, the natural variation that is created by having more study centers.
Q. And have you personally done any research on demographic differences between various locations?

A. Yes. Actually, I have a paper that reports on differences between body mass and mass index between various populations in various states in the United States actually. And there are very significant differences.

Q. How do those differences impact scientific research?

A. So, well, you're recruiting from a patient population in a particular state, U.S. state, and then you have to be -- that's fine. But if you are then doing a cross-study comparison and there are very significant health differences between the populations you're recruiting from, then you have to adjust for those.

As long as of course you do that careful statistical adjustment, then the results can be considered carefully analyzed.

Q. Overall, what is your opinion of Dr. Rettig's cross-study comparison analysis?

A. So he failed to show a significant difference, statistically significant difference. He ignores other Janssen studies that conflict with the results he highlights. And he failed to take into account the differences in the patient populations in the studies he compares.

Q. What do your opinions mean in terms of Dr. Rettig's ability to show that prednisone has an anti-cancer effect in combination with abiraterone?

A. This means that Dr. Rettig has not provided such evidence.

Q. Let's now turn to Dr. Rettig's argument about the phase III studies showing a survival benefit. And let's go through some more background information on clinical trial design.

What is the purpose of clinical studies?

A. Well, they initially are used to address dosing and safety issues and then ultimately efficacy questions about treatments.

Q. And how do clinical studies measure whether a treatment is effective?

A. Usually in the phase III study stage they are compared with a control or a standard treatment or a placebo.

Q. What are a studies' arms?

A. Okay. The arms represent the various treatments or placebos or controls, and patients are recruited in a randomized study into -- at random into those arms of the study.

Q. What is the purpose of a control arm in a clinical study?

A. It's to offer a comparison group and to measure the effect of the proposed new treatment against a comparison group.

Q. This slide refers to a placebo control and an active control in combination. Could you please define each.

A. A placebo control may be a pill that has the same texture and shape as the -- and color as the treatment pill, say, but only sugar, so not having any active -- any activity.

An active control could be a commonly used drug, the

standard of therapy. You could have a combination between an active drug of some type such as a steroid plus a placebo. Various combinations are possible.

Q. Dr. McKeague, could you please provide a single example of a clinical trial design.

A. So this is the basic design where a drug is compared against the placebo. So patients are recruited at random into one of the two arms, the treatment arm or the comparison arm, and followed until the endpoint; and their outcomes are compared.

Q. How does this study design allow one to measure the drug's effect?

A. Because this is -- this is comparing against placebo so if the drug has a beneficial effect, that should be noted -- that should be observed in the outcomes for those in the treatment arm.

Q. Now, Dr. Rettig's argument involves two phase III studies, the COU-AA-301 and COU-AA-302 studies. Is that your understanding?

A. Yes.

Q. And I'll refer to these studies as the 301 and 302 studies?

A. Yes.

Q. And did you consider the 301 and 302 studies in rendering your opinions for this case?

A. I did.
Q. Could you please describe the 301 and 302 studies for the Court.
A. They were both phase III studies, two arms in each. The patient population in the 00 -- sorry, the 301 study was chemo-refractory and the 302 study chemo-naive. The treatments in the comparison arms were the same in both; that is, both had the treatment arm consisting of 1,000 milligrams of abiraterone plus 10 milligrams of prednisone, and the comparison arm being placebo plus 10 milligrams of prednisone.
Q. Do the 301 and 302 studies show prednisone's anti-cancer effect when combined with abiraterone?
A. No.
Q. And why not?
A. Because prednisone is in both arms of the study; they're in the treatment arm as well as the comparison arm. Prednisone is in both arms, so any effect of prednisone is sort of canceled out; and the effect could be purely due to abiraterone.
Q. What were the 301 and 302 studies designed to investigate?
A. So they were designed to investigate -- well, compare prednisone plus abiraterone, the effect of that compared with prednisone alone.
Q. And moving to DDX 2300.55, could you please explain your point using this graphic.

A. Yes. So they're designed to assess the effect of abiraterone. As we see here in the graphic, in the treatment arm, the abiraterone plus prednisone; comparison arm, where abiraterone is replaced by placebo and prednisone is kept in the comparison arm. So --

Q. And -- I'm sorry.

A. -- this is a comparison, actually, of course, and designed to test whether abiraterone has an effect.

Q. So now moving to the next slide, could you please provide an example that illustrates why Janssen's phase III study design cannot show prednisone's effect?

A. Yes. Because say we -- say we replace prednisone with M&Ms, of course it's absurd to think that M&Ms would have an anti-cancer effect. So here we have exactly the same design but using M&Ms, and this of course just -- just ascertains abiraterone's effect. It can't assess the effect of M&Ms. Of course they don't have any effect anyway, but it can't assess the effect of M&Ms, only abiraterone.

Q. If abiraterone has an anti-cancer effect, could you say that the treatment arm of abiraterone in combination with prednisone has an anti-cancer effect?

A. So, pardon, could you repeat the question.

Q. Sure.

So do you understand that abiraterone has an anti-cancer effect?

A. I understand that.
Q. And if abiraterone has an anti-cancer effect, is it plausible to say that the combination of abiraterone and M&Ms would have an anti-cancer effect?
A. Very plausible, yes.
Q. And the study design could ascertain that effect of the combination but may not parse out the effect of M&Ms?
A. Exactly. So it's impossible to determine the effect of M&Ms on -- anti-cancer effect of M&Ms based on this design.
Q. Now, on DDX 2300.57, what design should Janssen have used to ascertain the anti-cancer effects of prednisone in combination with abiraterone?
A. This is the design hypothetical -- hypothetical study if actually carried out would actually assess that question, whether the combination of abiraterone and prednisone as compared with abiraterone and placebo.

So you see the prednisone now is removed from the comparison arm. Abiraterone is maintained in the comparison arm, then we can actually see the effect, the combined effect of abiraterone, prednisone compared with abiraterone.
Q. And just to make sure the record is clear, can we move back to DDX 2300.55. And Janssen's phase III studies involved a treatment arm of abiraterone and prednisone versus placebo and prednisone?
A. Yes, so this ascertains abiraterone's effect, this one.

Q. And now moving to the LATITUDE study, DDX 2300.58, which Dr. Rettig also relies on to make the same argument. Have you considered the LATITUDE study in rendering your opinions?
A. Yes.
Q. Could you please explain the design of the LATITUDE study.
A. Yes. It was a phase III trial. It had two arms. The patient population was newly diagnosed metastatic castration-sensitive patients. The treatment arm was 1,000 milligrams of abiraterone plus 5 milligrams of prednisone per day, and androgen deprivation therapy. And the control arm was just androgen deprivation therapy plus placebos.
Q. What does the LATITUDE study tell you about prednisone's anti-cancer effects in combination with abiraterone?
A. It can't tell you anything about that effect.
Q. Why is that?
A. Because, again -- yes. So, again, prednisone was in both arms.
Q. I'm sorry, could we --
A. Could you go back actually.
Q. Let's go back one slide --
A. I think I misspoke about that. Okay. So sorry. So the abiraterone was not in the control arm, so it's a comparison of the combination of abiraterone plus prednisone virtually against placebo because there's androgen deprivation therapy in there, so I misspoke. Let me correct that.

Q. Moving to DDX 2300.60, I think you may have just explained it, but can you please make clear what this study is designed to ascertain --
A. So --
Q. Please go ahead.
A. So this is essentially designed to ascertain the combined effect of abiraterone, prednisone versus placebo, but of course ADT is in both arms of the study, so any survival benefit here could be entirely due to abiraterone.
Q. Now moving to the next slide, could you please provide an example that illustrates why Janssen's phase III study design cannot show prednisone's effect?
A. Yes. So because using the same design except replacing the prednisone with M&Ms, which of course we know have no anti-cancer effect, we can still see an effect here because -- solely due to the abiraterone. So the M&Ms, yes, they're in there but they -- obviously it's absurd to think they could have an anti-cancer effect.
Q. Moving to DDX 2300.62. What design should Janssen have used to test the anti-cancer effects of prednisone?
A. So as I've talked about before, they should keep the abiraterone in the comparison arm. So here you see just replacing prednisone in the treatment arm by placebo, they could then do a comparison of this type which would -- as a hypothetical study if it could be performed, one could actually

address the question that this reversal resistance hypothesis is raising.

Q. So to summarize, how much information can you ascertain about prednisone's anti-cancer effects from the 301 and 302 phase III studies?

A. So these -- from looking at all these studies, they actually provide no evidence for an anti-cancer effect of prednisone when used with abiraterone. They weren't even designed to actually address the question of whether there is such an anti-cancer effect.

Q. Does that opinion, when you refer to phase III studies, also include the LATITUDE study?

A. It does.

Q. Let's now sum up your opinions. Dr. Rettig makes three arguments to which you respond. Can you please take us through those and your opinions on each.

A. Yes. So his first argument was based on anecdotal data from the dexamethasone extension study. He didn't provide any statistical analysis, anecdotes.

His second argument was based on this cross-study comparison of the two early-phase studies. He did an improper cross-study comparison, he didn't do any -- he didn't establish a statistical difference, and he didn't actually explain -- he didn't adjust the differences in the patient populations.

His third argument based on the phase III studies,

these various phase III studies, they weren't even designed to assess the anti-cancer effect of prednisone with abiraterone.

Q. What do your opinions mean in terms of prednisone's alleged anti-cancer effect when used in combination with abiraterone acetate?

A. So Janssen has failed to demonstrate that prednisone has an anti-cancer effect when used with abiraterone. I understand this means there's no direct infringement of the '438 patent Claim 1 and no unexpected results.

MR. SWANSON: Thank you very much for your testimony. I will now pass the witness.

THE COURT: Although we're drawing to the end of our trial day, let's get started on cross-examination.

MR. REIN: Your Honor, may I proceed?

THE COURT: Sure. Whenever you're ready.

(CROSS-EXAMINATION)

BY MR. REIN:

Q. Good afternoon, Doctor.

A. Good afternoon.

Q. My name is Tom Rein. We have not met before.

You presented at the beginning of your presentation a definition -- plaintiffs' definition of a person of ordinary skill in the art. I will just read the first part: A person of ordinary skill in the art with respect to the '438 patent is a physician specializing in urology or medical oncology who has

significant practical experience in the treatment of patients with prostate cancer.

Now, just so we're clear here, you are not a person of ordinary skill in this art, correct?

A. I am not a person of ordinary skill in the art, right.

Q. Your background is in mathematics and statistics, correct?

A. And biostatistics and clinical trials and analysis of data from clinical trials.

Q. You're not a medical doctor?

A. I am not a medical doctor.

Q. You have no training in oncology?

A. None.

Q. You have no training in urology?

A. No.

Q. And you have no training in endocrinology, correct?

A. I do not.

Q. You have never been involved in designing a clinical trial for prostate cancer, correct?

A. That's correct.

Q. Now, have you ever peer-reviewed or been part of a peer-review group for an oncology journal?

A. No.

Q. And the opinions that you provided in your expert report are based on your expertise in statistics, not clinical practice or knowledge or experience relating to the treatment

of prostate cancer, correct?
A. My opinions were through my expertise as a professor of biostatistics, which actually includes a lot of collaborations with medical teams and so on, and oncologists and medical experts of many, many different specialties.
And I also do a lot of review work. I review tenure cases at Columbia, for example, in the medical school, which obviously I read papers in these journals and papers submitted for review.
Q. Let me ask the question again. The opinions you provided in your expert report were based on your expertise in statistics, not clinical practice or knowledge or experience related to the treatment of prostate cancer, correct?
A. Well, I don't -- as you asked me before, I am not an expert in the treatment of prostate cancer. Does that answer your question?
Q. No, it really doesn't.
My question is, is it true that the opinions in your expert report are based on your expertise in statistics and not clinical practice or knowledge or experience relating to the treatment of prostate cancer, yes or no?
A. Wait a second. My knowledge you said? Or was -- what was the key word there?
Q. Well, let's take them one at a time. Your opinions were based on your expert -- on your expertise in statistics, true?

A. My profession is as a biostatistician, correct.
Q. Your opinions in your report were not based on experience in clinical practice, correct?
A. I'm not a clinician so I do not practice clinically. You're correct.
Q. And it's not based on your knowledge or experience related to the treatment of prostate cancer, correct?
A. Well, I read papers -- I've read -- for this case I have read lots and lots of papers on prostate cancer, I assure you.
MR. REIN: Your Honor, may I approach the witness with a deposition?
THE COURT: Have I got that?
MR. REIN: I don't know. I didn't -- I mean unless they provided it to you.
THE COURT: All right. Then show -- give them a copy if they don't have it, and I'd like copy as well if you have it.
(Discussion off the record between counsel.)
THE COURT: Just for the record, this is entitled Videotaped Deposition of Dr. McKeague dated July 28, 2017.
MR. REIN: Thank you, Your Honor.
BY MR. REIN:
Q. Dr. McKeague, do you have a copy of your deposition with you?
A. I do.

Q. Do you recall being sworn to tell the truth?
A. Of course.
Q. Could you please turn to page 27. Page 27, please. Specifically I'd like to --
A. Which page? There are various numbering here. You mean actually the page in the upper right-hand corner?
THE COURT: Yes, that's a good clarification. Are you referring to -- each 8 1/2 by 11 page has four mini pages on it. Are you talking about the mini page numbers?
MR. REIN: I am indeed, Your Honor.
THE COURT: Okay.
MR. REIN: Yes.
BY MR. REIN:
Q. Page 27, I would like to direct your attention to line 17.
Are you with me?
A. All right.
Q. I am going to ask, were you asked this question and did you give this answer?
"QUESTION: And the opinions that you provided in your expert reports are based on your expertise in statistics, not clinical practice or knowledge or experience related to the treatment of prostate cancer; is that correct?"
And your answer is: "That's correct."
Did you give that answer at your deposition, sir?
A. That's correct. I mean, but I think there's a big

possibility of misinterpretation of the word "knowledge," right? So -- so depending on what I understood in the context of this as what was meant by "knowledge." That's why I tried to clarify: What do you mean?

Was "knowledge" the key word? What knowledge are you referring to? Papers I've been reading about prostate cancer.

You have to be very, very careful and make things precise; otherwise, indeed, there will be variations in answer, sir.

Q. Well, Doctor, you expressed no such confusion at your deposition, did you?

A. Well, it depends on the context of what was going on at the time. In the deposition, it depends -- I would have to read more to see what the context was, but...

Q. You understand -- and I believe you testified to this on direct -- that events aren't always random, correct?

A. Wait a second --

Q. Events in the real world are not always random; sometimes they're influenced by other factors, correct?

A. Can you remind me of the exact statement.

Q. Well, why don't you tell us. Is every act in the real world random?

A. Wait a second. What is the context here? Every act? What are you talking about?

Q. Everything that you assess as a statistician, do you

assume that it's a random event a priori?
A. So do you want me to tell you what -- as a biostatistician, I analyze data? Is that what you're asking? Because data -- data come in many, many forms. I explained what the purpose of statistics and what the field of biostatistics does. And you seem to be expanding that into events in general, in the world, in the universe or something.
Q. I am asking you about events in the real world. Is every event random?
A. Well that's actually a kind of deep philosophical question.
Q. If you know one thing, then if there's a logical connection to something else, then the second event is not necessarily a 50/50 result, correct?
A. If you know something --
Q. Yes --
A. We're getting very vague here. I wish I could clarify exactly what you're saying, but --
Q. I'm asking you really a basic statistics question. If you have an event, X, and X and Y are related in a causal way, Y is not necessarily a 50/50 event, true?
A. Again, this so vague. It's on the level of philosophy, I guess. But then you're confusing it with -- well, I don't know. It's just a mixed-up question. Let me just say I don't understand the question.

Q. Fair enough.

Now, you do understand that based on the science, Dr. de Bono came up with a hypothesis that he went on to test, correct?

A. Well, I know he came up with a hypothesis, and it's in the Attard 2008 paper, reversal of resistance hypothesis.

Q. You heard his testimony about his hypothesis or you read it, correct?

A. Well, Dr. de Bono?

Q. Yes.

A. Actually, I wasn't in the courtroom when Dr. de Bono testified.

Q. Did you read his testimony?

A. I read -- I saw some part -- I read some parts of it, yes.

Q. What part of the testimony did you read?

A. Well, actually, you heard a little bit about that, about Dr. de Bono's testimony about variation, variability of PSA.

Q. Did you read the entirety of his testimony?

A. I received it rather late at night, and I must admit I didn't. I was very tired, and I didn't read the entire thing, no.

Q. Other than his testimony on PSA, did you read anything else?

A. I glanced -- well, it was very long. As I say, I was very tired. So I can't claim to have read it.

Q. Did you read his testimony on his extension study?
A. As I say, if you get a 300 -- I don't know how many pages it was. But I assure you I'm not going to start reading War and Peace at midnight.
Q. It's fine. I'm just following up on what you said on direct.
A. Okay.
Q. Now, you are aware that Dr. de Bono went on, because he was very impressed with the results from his extension study, and submitted the results to a number of oncology journals, correct?
A. Yes.
Q. One of the journals is the Journal of Clinical Oncology, correct?
A. Yes.
Q. Have you ever read -- before this litigation, have you ever read that journal?
A. I heard of it.
Q. Have you ever read it?
A. Not as part of my collaborative work with medical teams at Columbia, no.
Q. Do you know whether it's peer-reviewed?
A. Well, I did learn a little bit from Dr. Rettig's testimony about this journal. He has a high opinion of it. And he said it was peer-reviewed, so I have no reason to doubt his

statement.
Q. Is it common for oncology journals to have a peer-review staff that consists of scientists who know the subject matter?
A. Well, I can't speak to the peer-review process in this journal. I can -- I am pretty sure there is a rigorous peer review, but I can't -- I can't speak to details.
Q. Did the rigorous peer review tend to include biostatisticians?
A. Well, I've been asked to peer-review for medical journals, and sometimes I do; I agree to do it. It's -- so it's sometimes actually rather hard to find biostatistical reviewers, unfortunately. Because I've actually asked -- I'm on editorial boards myself, so they're in demand.
Q. Do you know whether the Journal of Clinical Oncology had a peer-review group that included a biostatistician?
A. Well, typically -- well, they probably have an editorial board that would then solicit reviews, referee reports from referees, experts in the field.
Q. Including statisticians, correct?
A. Indeed. They -- it is very possible. But I would say many, many medical journals, actually, sometimes don't do the due diligence and actually find a biostatistician referee. I've seen that for myself.
Q. You just said you had no reason to doubt Dr. Rettig's testimony that it's a very highly respected, high-impact

journal with a rigorous review process.
A. But I didn't hear Dr. Rettig say there was a bio -- as you say, a biostatistical review section. I didn't hear him testify to that effect.
Q. Would you expect that they, as part of the review process, they'd consult with a statistician?
A. I would hope they do. I would -- I have no -- no reason to know that they necessarily do.
Q. But you would expect that they do?
A. I would hope. I have no information. I have no -- Dr. Rettig, as I say, is -- what he told me, what I heard didn't say either way.
Q. Are you familiar with the Journal of Clinical Oncology?
A. Well, as I say, I've heard of it.
Q. I asked you about that one. My apologies.
What about the Journal of Cancer Research?
A. Heard of it.
Q. Have you ever read it?
A. Well, as a biostatistician, I don't typically read -- I subscribe to a lot of journals in my field. I don't routinely read papers from the medical literature unless they're involved in the studies that I'm doing.
So in this case, no, I haven't. I haven't read unless their paper's connected with this case.
Q. Would you expect that journal to be peer-reviewed?

A. I would hope -- well, again, from what I heard from Dr. Rettig, it's a reputable journal; and, therefore, I would expect it to be peer-reviewed in some sense.
Q. Are you familiar with the publication Cancer Cell Perspective?
A. No. Actually, that one I wasn't familiar with. But it is a -- well, the journal Cell is, of course, a very, very top journal, one of the three top journals. But I have no idea what this one is, even though it has "cell" in the title.
Q. Do you have any reason to doubt that it's a reputable, well-respected journal?
A. Well, actually, that one I hadn't -- I don't know. I don't know the connection to Cell or whether there is a connection. Dr. Rettig seemed to have a high opinion of it. But I have no independent opinion.
Q. In any event, you are, of course, aware that Attard 2008 and Attard 2009 were published in the Journal of Clinical Oncology, correct?
A. That's correct, yes.
Q. You would expect that -- and I think you testified that space is very valuable in that journal?
A. Indeed, yeah; in all journals.
Q. Right. And so they would only publish something that they believed had significance to practitioners, correct?
A. Well, they published -- they solicit referee reports.

They get referee reports. And if the referees do their due diligence -- if -- and if there were biostatistical reviewers, just as you -- we discussed, assuming all those things and they get good recommendations, one would think it would be published.

But sometimes referees fall short; they don't do due diligence. Maybe they couldn't come up with a biostatistical review, I have no idea. But you're just -- I'm just giving you the possible possibilities here.

Q. If they published in Attard 2008 and 2009 the de Bono study and findings, then you would expect that that was subjected to peer review, correct?

A. In some form or another. There's certainly the manuscript of the -- the main part of the manuscript, presumably, was subjected to peer review.

Most -- probably the most attention would be given to the primary objectives of the study. Sometimes referees may give cursory attention beyond that. But I can't read the minds of -- or speculate about -- we're just speculating about who the reviewers were or qualifications, all of these things.

But, yes, generally we trust journals to do the due diligence.

Q. If they thought that the data in it was just a bunch of noise, they would not have agreed to publish the publications, correct?

A. Well, so let's be careful here. The raw data, right -- you said "the data." There is underlying data from the studies, right --

Q. There's also --

A. -- that does not appear in the paper. So --

Q. The 2009 publishes a number of findings talking about the response rate of 4 out of 11 patients who received dex and then later received abiraterone and were not responsive to either, developed resistance. Then they were given dex and abiraterone together, and they responded. And that was reported as being a significant development, correct?

A. Well, it's interesting you say that because there is a short section on reversal of resistance which is maybe 10 lines. It's just a bland statement. It -- I didn't see anything in the papers saying the reversal of resistance hypothesis is proved -- is established, no. Nothing like that.

You know a referee, who knows? But the referees were, of course, looking at the study for what it was, as a phase I/phase II study. They -- the primary objective, as I understand it, was really on the phase I/phase II, not on the extension data, even though it appears there. It's true the hypothesis is stated in the Attard 2008.

Was the paper designed to test the hypothesis? There's a little bit of data, little bit of -- as you describe it. I talked about the anecdotal data on subject A and

subject B. So I'm sorry. I talked a lot about that in my direct, and I'm happy to clarify anything.

Q. I'm asking you questions. I'd appreciate if you would answer my questions.

My question was: If they didn't think that the extension study result was worthy of publication in that journal, they wouldn't have published it, correct?

A. Well -- so I talked about the supplement, the word "supplement," that these two patient -- the data on the two patients appeared in the web supplement. As I say, you can -- actually, I think I mentioned in my direct, web supplements are often not part of the rigorous review. There's simply not space to put everything you want in the papers, so it's relegated to the web supplement. Authors can put whatever they want there.

Q. Are you saying that the report on the extension study was all on the web supplement?

A. The evaluation of the reversal of resistance hypothesis. As I say, there was a little section in the paper. And --

Q. Let's stick with that.

A. -- you may -- if you read that paper, you would have to really be searching for something about reversal of resistance to say, Oh, yes, this is a result.

And I do not agree with that characterization.

Q. Doctor, they reported the findings, not in the appendix,

but in the major -- in the paper itself, correct?
A. Well, they reported -- they reported the outcomes of various patients in the extension phase.
Now, when you say "a result" -- and we're not talking about evidence that can rise to the level of statistical significance.
Q. Doctor, with all due respect, we will move this along much quicker if you can answer my questions with a yes, no. If they're -- if that's possible, I would appreciate it. You can elaborate in response to your own counsel's questions.
I'm just asking you a very simple question.
A. No. I'm happy -- I'm happy to answer your questions.
Q. The dex extension study, you said -- whatever you call it, the paragraph or so, the two paragraphs, that was in the main body of the paper, not the appendix, correct?
A. There was a description of the outcome, the salvage they called it, of some patients.
Q. That was in the main body --
A. Yes, it was in the main body. You're right. Yes. But is it a result? It's -- what do you mean by a "result"?
MR. REIN: Your Honor --
THE COURT: Wait a second. Wait a second. We can only bring out the information one piece at a time. So let's try to keep the answers a little bit shorter so we can do this in a little more of a Q-and-A format, okay?

MR. REIN: Thank you, Your Honor.
BY MR. REIN:
Q. If the peer reviewers thought that that portion of the study was garbage, they wouldn't have reviewed it, right?
A. Well --
Q. They wouldn't have included it, correct?
A. Well, as I say, I don't -- if the -- if the, if there was a claim in the paper that this information in that little section actually validated the reversal of resistance hypothesis, they would have paid attention to it, I'm sure. But as I say, it was -- there was no statement saying, Oh, therefore, this implies -- this means that the reversal of resistance hypothesis is validated, is confirmed. There was no statement like that.
Q. Let me ask you this: In your report, you did not indicate that you even consulted with an oncologist or scientist regarding the science or the results that were observed, correct?
A. No. I -- well, I read reports by, I think, Dr. Lipton in this case, who I understand is an oncologist. But certainly, I was provided with certain reports of that type.
Q. And you read reports, but you didn't consult with an oncologist or a scientist regarding the science or the results?
A. Well, that's true, yes. I didn't consult.
Q. Let's move on to confidence intervals, which you discussed

on direct.

THE COURT: You know what? Since this is a new subject area, why don't we take our break now and reconvene in the morning.

The cross-examination rule applies, as we know.

We'll resume at 9:00.

Now, tomorrow I anticipate we will meet until 1:00 or shortly thereafter. But I have some cases I've got to hear in the afternoon. So everybody should plan their lives accordingly.

Anything else we should deal with, though, before we break for the day?

MR. REIN: Not from our side, Your Honor.

MS. BLOODWORTH: No, Your Honor. I think we'll talk with plaintiffs about scheduling for the rest of the week.

THE COURT: Sure. Sure. Of course, I'll agree to anything reasonable.

You can step down, Doctor. Thank you.

See you in the morning.

(Proceedings conclude 5:15 p.m.)

FEDERAL OFFICIAL COURT REPORTER'S CERTIFICATE

I, **Rhéa C. Villanti, CCR, CRCR**, Official Court Reporter of the United States District Court for the District of New Jersey, do hereby certify that the foregoing proceedings are a true and accurate transcript of the testimony as taken stenographically by and before me at the time, place, and on the date hereinbefore set forth.

I further certify that I am neither related to any of the parties by blood or marriage, nor do I have any interest in the outcome of the above matter.

/S/Rhéa C. Villanti, CCR, CRCR 8/28/18

Official Court Reporter